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Stem Cells and Society

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STEM CELLS AND SOCIETY

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ABSTRACT

In recent years, therapeutic stem cell treatments and applications have become increasingly relevant to the medical community. Along with these developments, misconceptions, based on ethical and legal concerns, have arisen. This document offers an in-depth literature and research review into the development of stem cell treatments, along with an analysis of concerns from religious and political organizations. Our conclusion supports the continuation of all types of stem cell research and an increase in federal financial aid for future stem cell projects.

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PROJECT OBJECTIVES

The main purpose of this IQP project is to help the reader gain a greater understanding of the effect of stem cell technology on society. The project is divided into four different chapters, starting with chapter-1, giving the reader a greater understanding of the variety of stem cells currently known. The purpose of Chapter-2 is to exemplify the types of disease treatments that have been developed, documenting a variety of clinical trials and animal studies that have been administered, to provide examples of the benefits to society of stem cell technology. Chapter-3 gives the reader an in-depth look at the ethical concerns that surround this controversial subject, especially for embryonic stem cells, and shows how the embryo debates that began in the late 1970's with IVF technology now apply to the stem cell debate. The final chapter, Chapter-4, examines the laws and provisions that have been installed in the U.S. and other international countries that regulate stem cell and embryo use, as examples of the effects of politics and religion on science. The project ends with a conclusion regarding the use of stem cells in today's society, giving the author's opinions on the subject matter.

Chapter-1: Stem Cell Types

Sean Kelly

Stem cells are long-lived cells with the potential to differentiate into different types of cells. These remarkable cells act as an internal repair system for many tissues in the human body, and so physicians are interested in using them to treat various diseases. When stem cells divide, they can either create more stem cells, or they can differentiate into other cells having more specialized functions. Stem cells are truly unique in this sense; they are unspecialized cells capable of multiplying even after long periods of inactivity, and can be induced to divide into tissue or organ-specific cells with a much more determined function. The keyword there being: induced.

Stem Cell Classification

There are many types of stem cells. From an ethical standpoint, a common misconception is that there is only one type of stem cell and all research involving this stem cell destroys an embryo and is unethical. However, there are actually four main stem cell types. The most controversial type is a human embryonic stem cell (hESC) which, as the name suggests, is derived from human embryos. These cells are derived from 5-day old embryos prepared by in vitro fertilization (IVF), but no longer needed by the parents. The status of this embryo is the catastrophic issue that surrounds this type of stem cell. A common misconception about hESCs is that the embryo is killed *in vivo*, however this is far from the case and will be discussed later in this chapter. A second type of stem cell is the adult stem cell or the somatic stem cell. There are many types of adult stem cells including: the hematopoietic stem cells (HSCs), neural stem cells (NSCs), mesenchymal stem cell (MSCs), umbilical cord blood stem cells, epithelial stem cells,

and cardiac stem cells (CSCs). These are the five types of adult stem cells that will be discussed in more detail in this chapter. Until recently, these were the two main types of stem cells that scientists researched. However, within the last few years, two other new types of stem cells have been derived: induced pluripotent stem (iPS) cells and parthenogenic stem cells. iPS cells are differentiated skin fibroblast cells induced to a de-differentiated pluripotent state to become somewhat like ES cells. And parthenote stem cells are derived from unfertilized eggs stimulated to divide to the blastocyst stage from which ES cells are derived.

Stem cells are often classified by their potencies, their abilities to form other tissues. Some stem cells are more potent than others. There are essentially four levels of potency: totipotent, pluripotent, multipotent and unipotent. *Totipotent* cells can make any cell in the adult body plus extra-embryonic tissues such as the placenta. Examples of totipotent cells are newly fertilized zygotes, or the embryo through the 8-cell stage. These cells cannot make cell lines, so scientists do not use them for medical therapies where large numbers of cells are required. *Pluripotent* cells can make every tissue in the body except the placenta. A common misconception is that ES ells are totipotent; however ES cells are actually pluripotent. A *multipotent* stem cell has the ability to form a few related cell types. One example is hematopoietic stem cells that can differentiate into several kinds of blood cells, but usually cannot form a neuron. *Unipotent* stem cells have the potential to form one other type of cell, and that type is usually the tissue they come from. A good example of this type of stem cell is a skin stem cell that usually forms more skin. Potency plays a huge role in considering which types of stem cells are used for specific medical therapies.

Embryonic Stem Cells

The stem cell with the most medical potential is also surrounded by the most controversy, the ES cell. First and most importantly, ES cells are not derived *in vivo*. Rather, human ES cell lines are derived outside the body from embryos produced by *in vitro* fertilization (IVF) (Yu and Thomson, 2006). This process involves introducing donated oocytes and sperm to each other in a culture dish. *In vitro* fertilization embryos are initially prepared in reproductive clinics for couples who are having trouble having children. The IVF process is not efficient, so excess embryos are prepared. Once the couple has enough children, the remaining IVF embryos are either destroyed or are donated for research with the couple's consent. Currently in the United States there are approximately 400,000 IVF embryos in frozen storage of which about 2.8% will be discarded. The debate about what to do with the *excess* IVF embryos is not new, but has been around since the birth of the world's first IVF baby in 1978 (BBC News, 1978). The ethical status of excess IVF embryos is the center of the stem cell debate, not *in vivo* experimentation.

ES cells were first derived in mice in 1981 (Evans and Kaufman, 1981). In the 1990s, stem cell lines were derived from two non-human primates (the rhesus monkey and the common marmoset), which gave researchers a much closer model to humans for the derivation of hESC. In 1998, the first human ES cell line was prepared (Thomson et al., 1998). Mouse ES cells and human ES cells were both prepared from IVF embryos. The embryos were grown about 5 days to the blastocyst stage. The blastula consists of an outer trophoblast layer of cells and an inner layer termed the inner cell mass. ES cells are taken from the inner cell mass. The ES cells were plated onto a layer of mouse fibroblast feeder cells in bovine serum. For the mouse ES cells, bone morphogenetic proteins (BMPs) and leukemia inhibitory factor (LIF) were added to the serum to help maintain their undifferentiated pluripotent state, and the ES cells began to

proliferate. BMPs help induce the inhibitor of differentiation protein (Id), the inhibitor of extracellular receptor kinase, and p38 mitogen-activated protein kinases. For human ES cells, the LIF/STAT3 pathway seems to be inactive in undifferentiated stem cells, and the addition of BMPs causes rapid differentiation (Yu and Thomson, 2006).

Currently, scientists are working to develop ES cell culture conditions that reduce the exposure of the cells to non-human factors, as some scientists worry about the possibility of the feeder layer cells becoming infected with animal viruses which would infect the ES cells prior to therapy. Scientists have reported that activation of the Wnt pathway by 6-bromoindirubin-3'-oxime (BIO) promotes ES cell self-renewal when bFGF (basic fibroblast growth factor), Martrigel (mixture used to resemble the extracellular matrix found in many tissues, used as a substrate) and a proprietary serum replacement product is present (Yu and Thomson, 2006). bFGF, TGFβ (transforming growth factor beta: a secreted protein that is responsible for many cellular functions, including the control of cell growth, cell proliferation, cell differentiation, and apoptosis), and LIF, can support some human ES cell lines in the absence of feeder cells (Klimanskaya et al., 2005). Researchers are questioning how well these new culture conditions will support various ES cell lines, but the finding provides hope that a set of culture conditions not involving feeder cells will soon be determined. The ideal human ES cell medium would consist of defined components that are not originated in animals, provide a way to minimize genetic and epigenetic changes in culture, provide a cost-effective simple use, and provide a way to allow cell growth at clonal densities (Yu and Thompson, 2006).

One key problem using ES cells for therapy is they are genetically related to the egg and sperm donors, but not to the patient. The holy grail in stem cell research is to derive truly pluripotent cells that are genetically identical to a patient so those cells will not be rejected by the

patient. There are two ways to achieve this: somatic cell nuclear transfer (SCNT) or by iPS cells (discussed later). The first derivation of a human ES cell line using SCNT was reported in 2005 by a South Korean group (Hwang et al., 2005). SCNT involves transferring genetic information from a somatic cell (usually a skin fibroblast nucleus) into an unfertilized egg cell whose nucleus has been removed. This transfer allows an embryo to form that is genetically identical to the skin cell donor (patient). The embryo is cultured in vitro for 5 days to the blastocyst stage, then ES cells are taken from the inner cell mass. Unfortunately, this exciting landmark finding was later retracted due to fraud, so the scientific community still awaits the first human SCNT success. Recently, scientists have produced a patient's triploid ES cell line derived by injecting a diploid fibroblast nucleus into a nucleated haploid egg, but the triploid ES cells are not suitable for therapy (Coombs, 2011).

Little is known about the factors that make ES cells pluripotent while other stem cells are only unipotent. Oct4, a transcription factor, is a key marker for hESCs. The expression of this transcription factor has been shown to help maintain ES cells in an undifferentiated state, but only expressing this gene is insufficient for the control. Recently, another transcription factor, Nanog, has been shown to be critical for maintaining the pluripotency of mouse ES cells (Yu and Thomson, 2006). Nanog is indeed expressed in human ES cells, but at a much lower level than in mouse, and its function has yet to be determined. Upon comparing total gene expression patterns between ES cell lines, ES cells, adult stem cells, and differentiated cells, the identification of genes important to ES cells has been accomplished (Tanaka et al., 2002). One key factor is Esg-1, which has been found to be associated with pluripotency in mouse ES cells (Tanaka TS, Kunath T, Kimber WL, 2002). Thus, slowly the route to determining key stem cell markers has started.

Scientists are also working on ways to genetically manipulate ES cells to introduce new genes into patients by gene therapy. For example, genes encoding adenosine deaminase (ADA) could be inserted into patients lacking ADA to correct the disorder Severe Combined Immunodeficiency Disease (SCID). This form of genetic engineering has the ability to insert a specific cloned gene into an ES cell by electroporation, transfection by lipid-based reagents, or infection by lentiviral vectors. Homologous recombination can be used to specifically replace host genes with new ones. This technique has recently been successfully developed for human ES cells, and is therefore opening new opportunities for uses in gene therapy.

The uses for human ES cells seem endless. Once they can be controlled in culture and differentiation, these cells have the potential to replace or rebuild damaged tissue cause by injury or diseases, such as diabetes, myocardial infarctions, Parkinson's disease, or even spinal cord injury. Deriving patient-specific ES cells and controlling their differentiation remain the biggest challenges.

Adult Stem Cells

This type of stem cell can be derived from various parts of a child or adult body, and its function depends on where in the body the cell is located. Common types of adult stem cells (ASCs) are found in bone marrow, skin, and brain. Some studies indicate that ASCs may be more potent than originally realized, and can differentiate into many different cell types. Research on ASCs is important as possible replacements for ES cells, however ASCs do not grow as well as ES cells and they are not as potent. But they can be patient-specific and will be genetically identical to donor (Kadereit, 2012). Just about all tissues in the body contain adult stem cells that restore their respective tissue. The types discussed in this chapter are:

hematopoietic stem cells (HSCs), neural stem cells (NSCs), mesenchymal stem cells (MSCs), umbilical cord blood stem cells, epithelial stem cells, and cardiac stem cells (CSCs).

Hematopoietic Stem Cells

Hematopoietic stem cells (HSCs) are found mainly in bone marrow, and serve the body by providing blood cells for transporting oxygen and fighting infections. HSCs are easy to obtain by either taken directly from the bone marrow or can be stimulated to transfer into the peripheral blood stream using hormones. This type of stem cell was the first to be used for therapies; bone marrow was first used in 1957 to treat leukemia patients (Thomas et al., 1957). HSCs have been used to treat blood cancers like leukemia and lymphomas for over 50 years. More recently, they have been used to treat breast cancer and heart attack patients. HSCs potential to differentiate into other cells other than blood is under intense research.

Neural Stem Cells

A couple of decades ago, rebuilding the nervous system with stem cells would have been considered impossible. And then in 1989, scientists discovered neural stem cells (NSCs) (Temple, 1989). In their undifferentiated state, NSCs are similar to cells found in a developing fetus that initially form the brain and spinal cord. Research suggests that these stem cells can differentiate into most, if not all, of the cells found in the brain, including neurons and glia. The ability of these cells to repair degenerative diseases such as Parkinson's, amyotrophic lateral sclerosis, or degenerative injuries is promising. There are currently two approaches for using these cells: either isolate the cells and grow them in culture, or stimulate endogenous NSCs in the brain to proliferate. Stem cell proliferation occurs in two main locations in the brain: the

subventricular zone (the layer of cells surrounding the ventricles), and the dentate gyrus of the hippocampus (where new neural cells are formed) (Bethesda, 2009). By the mid-1990s, research had shown that when the brain is damaged, stem cells in these two areas proliferate, differentiate, and migrate to the area of injury.

Research into ways for stimulating endogenous NSCs in the brain to begin dividing has shown that delivering transforming growth factor-alpha (TGFα) enhances the brain's own repair mechanism using the stem cells it already contains (Bethesda, 2009), but more research in this area needs to be performed.

Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) are found in bone marrow (in addition to HSCs), and are capable of forming a wide range of mesodermal cell types, including fat cells, muscle cells, skin cells, nerve cells, cartilage, bone, tendons, and ligaments. This type of stem cell has been researched since the 1970's (Friedenstein, 1976), and is the best characterized type of stem cell after HSCs. Researchers have sufficient information on this stem cell type to isolate them, amplify them, and produce MSC lines in culture. Unlike other adult stem cells, MSCs can easily be attained in appropriate quantities for clinical applications. Scientists are now investigating the molecular pathways that control their growth and differentiation.

Some clear benefits of this stem cell type include its ability to express introduced genes (for use in gene therapy), and their ability to be frozen without losing their multipotent state (this allows for "off-the-shelf therapy approaches (Kadereit, 2012). Trials using animal models are already underway involving the reconstruction of cartilage, bone, muscle (including heart muscle), and tendons. These cells provide great hope for human implications.

Umbilical Cord Blood Stem Cells

Immediately after birth, doctors now ask the parents if they wish to bank the baby's umbilical cord blood cells. Similar to bone marrow, umbilical cord blood is an abundant source of hematopoietic stem cells. This type of hematopoietic stem cell is more primitive than marrow HSCs, so are less likely to be rejected by a patient (Viacord, 2011). They are also easier to obtain than marrow cells. In several countries around the world, cord blood is kept in storage either publically or privately for research. This stem cell type has already been used for medical procedures for diseases like leukemia. One disadvantage for this type of stem cell is the limited number of total HSCs per cord.

Epithelial Stem Cells

Another type of adult stem cell can be found in the basal layer of skin, and are known as epithelial stem cells (ESCs). They are found in the self-renewing areas, such as the hair follicle of the epidermis (**Figure-1**). In the hair follicle, the stem cells are located in two main area, the base (shown as green in the diagram) and in the bulge near the surface (shown in pink in the diagram). A hexagonal bulge that lies beneath a single squame is the "epidermal proliferative unit" (EPU) (Cotsarelis, 2006). The central cell within the EPU creates proliferating cells known as transient amplifying (TA) cells. The TA cells move laterally, then differentiate and move upward within the epidermis to help replace surface cells. In addition to the regenerative nature of TA cells, there is another cell deeper within this layer of skin that obtains the same regenerative purpose but has different function. Hair follicle stem cells located deep in the papilla cyclically regenerate the lower portion of the follicle itself. These stem cells are assumed to located in the "secondary germ" at the base of the telogen hair follicle. It has been understood

that the secondary germ travels down the hair bulb during anagen (diagram upper left) and provides stem cells to produce more hair (Cotsarelis, 2006). Of all the mature basal cells, it has be estimated that 5% are able to reproduce rapidly and are the epithelial stem cells. Research needs to be conducted to establish clear differences between the two types of epithelial stem cells, and to understand the signals that initiate their differentiation so treatments can be developed for various skin diseases.

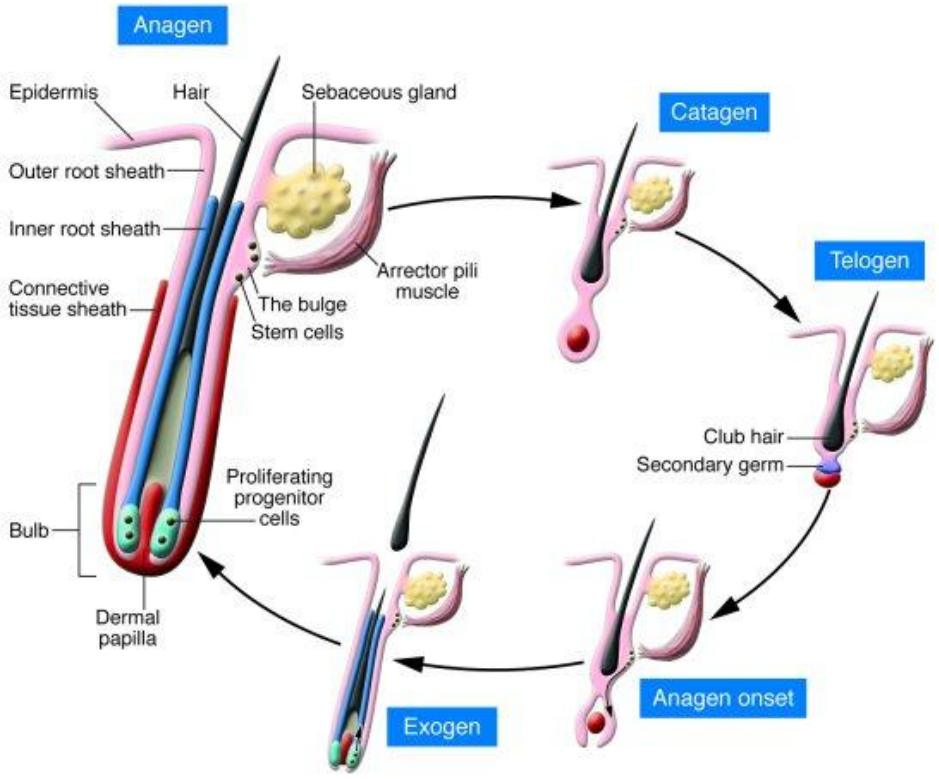

Figure-1: Diagram of Stem Cells Present in Hair Follicles. The figure shows the various stages of hair growth, including anagen, catagen, telogen, and exogen. Stem cells are located in the upper bulge and at the base of the dermal papilla. Reproduced from: http://www.jci.org/articles/view/27490/figure/1

Cardiac Stem Cells

The final adult stem cell to be discussed is the cardiac stem cell (CSC). These cells have been localized in mouse, rat, and human hearts, and include c-Kit+ cells (Beltrami et al., 2003) and Isl1+ cells (Laugwitz et al., 2005). These cells allow the heart to repair minor damage, and may have applications for treating heart attack patients (Touchette, 2004). The plan is to inject the diseased or damaged heart tissue with CSCs to regenerate the heart back to its original functionality. CSCs have been found in the interstices between the muscle cells in the hearts of rats. After culturing the cells, they were implanted back in the heart, and 70% of the heart reformed within 20 days (Touchette, 2004). An even better procedure is under investigation for stimulating CSCs already present in a patient's heart. Solidifying the potential of these stem cells would provide a remarkable breakthrough in the treatment of heart disease.

iPS Stem Cells

A new area of remarkable research involves the derivation of adult stem cells by reprograming them into pluripotent cells. This reprogrammed cell is known as an induced pluripotent stem (iPS) cell. These cells were first induced from mouse skin fibroblasts (Takahashi and Yamanaka, 2006) and later with human skin fibroblasts (Takahashi et al., 2007). Shinya Yamanaka's lab of Kyoto University in Japan discovered the ability to reprogram skin fibroblast cells. In his initial experiments, he used retroviruses to deliver four key genes into skin cells to reprogram them to a pluripotent state. If these cells are truly pluripotent, they might serve as replacements for embryo derived ES cells, while destroying no embryos and being genetically identical to the patient.

However, the initial four genes used for reprogramming included *c-Myc* which is an oncogene, and in some instances iPS cells implanted into mice developed tumors. So the research shifted to eliminating *c-Myc* in the reprogram (Kim et al., 2008). Also, when retroviruses are used to deliver the genes, they insert genes randomly which can disrupt important genes or switch on oncogenes. So some research has focused on doing the reprogramming without using retroviruses (Stadtfeld et al., 2008). Biologists have also been working on using adenoviruses to deliver the reprogramming genes, which will eliminate the concern of retroviral injection into the cells, or packing the genes into a "piggyBac" transposable element that has the ability to move out of the chromosomes once the cellular reprogramming is complete. Another exciting possibility takes genes out of the equation entirely, and delivers the proteins encoded by the genes instead (Reprogramming, 2009). The proteins that the original genes encode are actually the initators of the reprogramming, so Sheng Ding of Scripps Research Institute in La Jolla (California) decided to deliver them directly. The key component of this procedure is ensuring that enough proteins make it into the target cells. To do this, Ding and his team attached each protein to polyarginine, a molecule consisting of 11 copies of arginine attached end to end. These molecules can easily cross cell membranes with any proteins that are attached to it making it ideal for delivery into cells. Ding's team removed fibroblasts from connective tissue in mouse fetuses and soaked them with four polyarginine-tagged proteins for 12 hours, then removed these proteins for 36 hours and then reintroduced them. This was performed four times, and two weeks later colonies of iPS cells we extracted from the culture (Aldhous, 2009). This method poses no threats of cancer developing because the reprogramming proteins are broken down quickly after reprogramming has been achieved. With the success of

this experiment, the next course of action includes increasing the efficiency of the process, so Ding's team is testing valporic acid which appears to increase efficiency.

The main remaining question for iPS cells is whether they are truly pluripotent and can replace embryo derived ES cells in therapies. Some scientists have reported that iPS cells contain mutations in their DNA (Gore et al., 2011), and are not pluripotent (Hayden, 2011). So, more research is needed to see if they are potent enough to heal tissues. Once emerging from this stage of research, it is clear this technology will bring about a great medical and scientific accomplishments resulting in cures and therapies for many degenerative diseases and tissue injuries.

Chapter-1 Works Cited

Aldhous, Peter (2009) Reprogramming offers hope of safer stem cells. http://www.newscientist.com/article/dn17008-reprogramming-offers-hope-of-safer-stem-cells.html

Beltrami AP, Barlucchi L, Torella D, Baker M, Limana F, et al. (2003) Adult Cardiac Stem Cells Are Multipotent and Support Myocardial Regeneration. *Cell*, 114: 763-776.

Bethesda (2009) Chapter-8: Rebuilding the Nervous System with Stem Cells. National Institutes of Health. http://stemcells.nih.gov/info/scireport/chapter8

Coombs, Amy (2011) New Way to Make Embryonic Stem Cells. *The Scientist*, October 5, 2011. http://the-scientist.com/2011/10/05/new-way-to-make-embryonic-stem-cells/

Costarelis, George (2006) Epithelial Stem Cells: A Folliculocentric View. *Regenerative Medicine.* http://www.med.upenn.edu/timm/documents/JIDfolliculocentricReview.pdf

Evans MJ, Kaufman MH (1981) Establishment in culture of pluripotential cells from mouse embryos. *Nature*, 292: 154-156.

Friedenstein AJ (1976) Precursor Cells of Mechanocytes. *International Review of Cytology*, 47: 327–359.

Gore A, Li Z, Fung H, Young J, Agarwal S, et al. (2011) Somatic Coding Mutations in Human Induced Pluripotent Stem Cells. *Nature*, 471: 63-67.

Hayden, Erika Check (2011) The Growing Pains of Pluripotency. *Nature,* 473: 272-274.

Hwang WS, Roh SI, Lee BC, Kang SK, Kwon DK, Kim S, Kim SJ, Park SW, et al. (2005) Patient-specific embryonic stem cells derived from human SCNT blastocysts. *Science,* 308: 1777-1783.

Jones NL (2003) The Stem Cell Debate: Are Parthenogenic Human Embryos a Solution? http://www.washingtonpost.com/ac2/wp-dyn/A18046-2001Dec9?language=printer

Kadereit, Suzanne (2012) Adult Stem Cells. International Society for Stem Cell Research. http://www.isscr.org/public/Adult_SC.pdf

Kim JB, Zaehres H, Wu G, Gentile L, Ko K, et al (2008) Pluripotent Stem Cells Induced from Adult Neural Stem Cells by Reprogramming with Two Factors. *Nature,* 454: 646-650.

Klimanskaya I, Chung Y, Meisner L, Johnson J, West MD, Lanza R (2005) Human Embryonic Stem Cells Derived Without Feeder Cells. *Lancet,* 365: 1636-1641.

Laugwitz KL, Moretti A, Lam J, Gruber P, Chen Y, et al. (2005) Postnatal Isl1+ Cardioblasts Enter Fully Differentiated Cardiomyocyte Lineages. *Nature,* 433: 647-653.

Tanaka TS, Kunath T, Kimber WL, et al. (2002) Gene expression profiling of embryo-derived stem cells reveals genes associated with pluripotency and lineage specificity. *Genome Research,* 12: 1921-1928.

Reprogramming Offers Hope of Safer Stem Cells (2009) *NewScientist.* http://www.newscientist.com/article/dn17008-reprogramming-offers-hope-of-safer-stem-cells.html

Stadtfeld M, Nagaya M, Utikal J, Weir G, and Hochedinger K (2008) Induced Pluripotent Stem Cells Generated Without Viral Integration. *Science,* 322: 945-949.

Takahashi K, and Yamanaka S (2006) Induction of Pluripotent Stem Cells From Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors. *Cell,* 126: 663-676.

Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, Yamanaka S (2007) Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors. *Cell,* 131: 1-12.

Temple S (1989) Division and Differentiation of Isolated CNS Blast Cells in Microculture. *Nature,* 340: 471–473.

Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, Jones JM (1998) Embryonic Stem Cell Lines Derived From Human Blastocysts. *Science,* 282: 1145-1147.

Touchette N (2004) Stem Cells Found in the Heart.
http://www.genomenewsnetwork.org/articles/10_03/cardiac.shtml

Viacord (2011) www.viacord.com

Weiss, Rick (2001) 'Parthenotes' Expand the Debate on Stem Cells.
http://www.washingtonpost.com/ac2/wp-dyn/A18046-2001Dec9?language=printer

Yu J, and Thomson JA (2006) Embryonic Stem Cells. *NIH Publication*. Bethesda.
http://stemcells.nih.gov/staticresources/info/scireport/PDFs/Regenerative_Medicine_2006.pdf

Chapter-2: Stem Cell Applications

Michael Boyd

Over the past century, the development of stem cells as an application in medical research has led to several significant medical advances and the advent of the field of regenerative medicine. The discovery and application of stem cells in medical research has helped shape the care of patients in today's hospitals, and will continue to shape patient care in the future. Many diseases and ailments are currently being successfully treated using stem cell technology, and through further development many more may be treated. A few of the most actively researched ailments treated with stem cells include leukemia, Parkinson's disease, diabetes, vision impairment and heart tissue injuries. Countless other ailments exist that stem cells may eventually be used to treat, but additional research is required. The purpose of this chapter is to describe how stem cells are currently being used to treat several example diseases, as this will lay the foundation for helping determine their "societal benefits" in later chapters on ethics and legalities.

Stem Cell Treatment of Leukemia

At the turn of the 20th century, a greater interest within the medical community concerning stem cells developed when researchers discovered that all varieties of blood cells originated from one type of undifferentiated cell. The specific identity of this undifferentiated blood parent cell was not fully understood until 1963 when two Canadian scientists, Ernest A McCulloch and James E. Till, documented the self-renewal potential of transplanted mouse bone marrow while working at the Ontario Cancer Institute (McCulloch & Till, 2005). This

groundbreaking discovery led to the further development and research of these hematopoietic stem cells around the world, and they are currently the best characterized of all stem cell types.

One of the most successful disease treatments with stem cells has been seen with leukemia and other blood ailments. Leukemia is a malignant cancer of the blood and bone marrow (Ludwig, 2009). Leukemia, or blood cancer, is a disease that is caused when the body produces too many immature white blood cells. According to the Leukemia and Lymphoma Society, nearly 45,000 people are diagnosed with leukemia in the United States every year (Leukemia, 2012). Leukemia was very lethal before the use of stem cell treatments, with a death rate of approximately 86% of those diagnosed from 1960 to 1963. Today, modern stem cell treatments have contributed to a significant decrease in lethality to 43% (from 2001 to 2007) (Leukemia, 2012). Leukemia results from a mutation in the DNA of primitive blood forming cells (hematopoietic stem cells, HSCs) which then produce high quantities of immature white blood cells. HSCs are located in the bone marrow (and other places), so to cure leukemia, the patient's diseased HSCs must be destroyed by radiation or chemotherapy, and then fresh compatible HSCs provided to the patient from a donor.

The earliest successful method of leukemia treatment using stem cells is through the transplantation of bone marrow. A donor's bone marrow is extracted from a bone in his/her body and is transplanted to a sick patient, who has gone through chemotherapy prior to the transplant to eliminate his diseases HSCs. The transplant replaces the patient's infected or diseased bone marrow, allowing the HSCs to differentiate into normal specialized blood cells (Bone Marrow Transplant, 2012). This bone marrow transplant method was first developed by Dr. Edward Donnall Thomas in 1957, working at Mary Imogene Basset Hospital in Cooperstown New York (Thomas et al., 1957). Dr. Thomas' work showed that a complete remission of leukemia could be

achieved. His earliest 1957 paper claimed that a bone marrow transplant could be performed with identical twins because the bone marrow was easily identifiable as histo-compatible between them. Dr. Thomas moved in 1963 to the University of Washington, and in 1969 performed the first successful bone marrow transplant on a patient with advanced leukemia. The procedure was performed with one sick and one healthy set of identical twins, known as a syngeneic transplant. Since these initial procedures on twins, advances have been made in the procedure that allow non-related patients to be matched, known as an allogeneic transplant, in which patients and donors are matched through blood type (Raju, 2000). It is imperative that the donor/patient pair have a bone marrow match; otherwise, the sick patient can fall ill to graft-versus-host disease (GVHD) in which the patient's immune system rejects the foreign bone marrow. Significant steps have been taken to match leukemia patients with potential donors; the National Bone Marrow Donor Registry (NMDP) was established in 1986 and matches an estimated 200 unrelated patients per month (Deeg et al., 2001).

In addition to providing HSCs to leukemia patients using bone marrow transplants, peripheral blood stem cells and umbilical cord blood stem cells can also be used (Types of Bone Marrow Transplants, 2009). These three types of treatment differ from one another, although the main goal is to provide HSCs for transplantation into sick patients. A peripheral blood stem cell transfusion is a less invasive and less complicated. The identification of HSCs in peripheral blood was discovered in 1990's, and has made stem cell transplants for leukemia patients less invasive. HSCs can be stimulated in patients using hormones to move from the bone marrow into the peripheral blood from which they are isolated for a patient (Mayer et al., 2003). Chemokine, a growth inducing hormone, is intravenously administered to a donor before harvesting the peripheral blood. Chemokines induce a rapid cell mobilization; the HSCs leave

the bone marrow and reproduce quickly, allowing transfusion. The patient is connected to a machine that enriches the HSCs from the donor's blood, and then the blood is returned to the donor (Rosenbeck et al., 2010). This peripheral blood procedure's popularity has far surpassed that of bone marrow donation, and has helped save numerous patients with blood based ailments.

The third way of gathering HSCs for treating leukemia is from umbilical cord blood (UCB). In 1988, Dr. Elaine Gluckman of L'hospital St. Louis in Paris performed the first successful umbilical cord blood transplant on a 6 year old boy (discussed in Wagner and Gluckman, 2010). It was determined that UCB could be harvested from unmatched donors and used to transplant into sick patients, working in the same manner as other types of HSC cell transfusions. The first test performed on an unrelated donor/patient using umbilical cord blood was in 1993 (Gonzalez-Ryan et al., 2000). In a November of 2011 a test was performed at the Eurocord Hospital St. Louis which compared the survival rate and percentage of graft-versus-host disease (GVHD) between related and unrelated UCB transplants. It was determined that unrelated transfusions showed a higher rate of GVHD (Frey et al., 2009). Although GVHD was still present, the amount of rejection was found to be less prominent from HSCs extracted from umbilical cords versus bone marrow. This may be because UCB stem cells are not as "educated" or differentiated as similar cells present in bone marrow (Gonzalez-Ryan et al., 2000).

Stem Cell Treatment of Parkinson's Disease

Parkinson's disease (PD) is a nervous system disorder characterized by uncontrollable shaking, tremors, and loss of muscle control. PD is typically diagnosed in patients over the age of 50, although there have been rare cases occurring in younger patients. Parkinson's disease is caused by the deterioration of nerve cells in the *substantia nigra* area of the brain that produce

dopamine, the chemical neurotransmitter used to signal muscle movement throughout the body. Currently, there is no cure for PD and its cause remains unknown (Zieve & Eltz, 2011a). Some treatments currently exist, such as Levodopa (L-DOPA), which helps sustain dopamine levels by providing a chemical precursor to dopamine, but these drugs stop working after a few years and can cause debilitating complications (Takahashi, 2007). The use of stem cells to generate dopamine-producing neurons could provide a cure and save thousands of lives.

Currently, there are two stem cell approaches for the successful treatment of rodent (mouse and rat) PD models, but these treatments have not yet been fully evaluated for treating human PD patients. The first approach developed involved the transplant of adult neural stem cells (NSCs) into the *substantia nigra* area of a living rat brain. In 1998, the first successful procedure was performed on rats, and was found to significantly improve their PD symptoms (Studer et al., 1998). In 2009, Stephen Ertelt performed the successful transplant of adult NSCs into one human PD patient, who achieved some improvements. The greatest accomplishment of this procedure was that the treatment produced no teratoma tumors (Ertelt, 2009). The transplant of adult NSCs without the production of teratoma tumors is very important, as it shows that it is possible to transplant neurological stem cells successfully that will not continue growing indifferently, and this is not always the case with ES cells. As discussed in Chapter-1 though, adult NSCS are difficult to work with because they are rare in tissues and they are hard to grow, which makes the continuation of Ertelt's work challenging.

The second procedure involves the artificial growth of embryonic stem (ES) cells and their transplant into the *substantia nigra*. In theory, the insertion of ES cells into the *substantia nigra* stimulates the ES cells to differentiate into dopamine-producing neurons. Since 2002, this approach has been successful to a minimal degree in rat models (Bjorklund et al., 2002; Kim et

al., 2002; Ryan, 2004). As discussed in Chapter-1, scientists prefer working with ES cells because they have a greater growth potential than adult stem cells, but they have ethical issues. So far, human ES cells have only been shown to differentiate into dopamine producing neurons *in vitro*, but have not been used for clinical trials with PD patients (Perrier et al., 2004).

ES cells are pluripotent, and can differentiate into any cell in the adult body, including dopamine-producing neuronal cells (Yang et al., 2011). However, some experiments performed with ES cells in animals noted they can sometimes form teratoma-like tumors. For example, the first PD animal experiment, performed in 2002 by Lars Bjorklund at Harvard Medical School, showed that injecting small numbers of ES cells into a rat produced fully differentiated dopaminergic neurons in 56% of the injected rats. However, the remaining 44% developed "teratoma-like tumors" or showed no graft survival (Bjorklund et al., 2002; May, 2002). The ES cells that have not differentiated create tumors for some unknown reason, causing complications for the rats (Takahashi, 2007). According to Yang, the success of an ES graft depends on several factors, including ES "cell purification, the particular ES population, or the specific induction protocol" (Yang et al., 2011).

Although most of our current PD success stories come from research on rodent models, the ability of human ES cells to differentiate into dopaminergic neurons (Perrier et al., 2004) provides hope for a cure for Parkinson's disease in patients. If researchers are able to develop a method which inhibits ES cell tumor growth and deal with the ethical issues involved with embryo destruction (explained more thoroughly in Chapter-3), a treatment or cure for Parkinson's disease using stem cells is very plausible.

Stem Cell Treatment of Diabetes

According to the World Diabetes Foundation, as of 2010 an estimated 285 million people are living with diabetes worldwide. With the trends of obesity and other unhealthy behaviors, this estimation is expected to grow to 438 million by 2030 (Diabetes Facts, 2012). Insulin is the body's hormone that helps regulate the uptake of glucose from the bloodstream by tissues. Diabetes is caused when insulin is either not produced in the body at high concentrations, or the body becomes resistant to insulin, resulting in less uptake of glucose into tissues and elevated blood sugar. Diabetes causes high blood pressure, and if untreated can lead to other severe complications including amputation of limbs or death. There are two main types of diabetes, type I and II. Type I diabetes is caused by the destruction of pancreatic β cells (which synthesize insulin) by a patient's own immune system. Following the destruction of pancreatic tissue, an insufficient production of insulin causes a decrease in uptake of glucose into tissues and elevated serum glucose. This type of diabetes is a lifelong ailment, and the patient must administer insulin shots everyday as needed. Type II diabetes; on the other hand, is characterized by a resistance to insulin in the body. In this case, the cells respond less to the insulin that is produced, so the tissues do not take up as much glucose (Zieve & Eltz, 2011b). Type II diabetes can sometimes be treated by diet and exercise, which restores insulin sensitivity.

With respect to stem cells treatments for type-I diabetes to replace insulin producing cells, the results so far are similar to Parkinson's disease in which most of the experiments have been performed in diabetic animal models. Some of the earliest experiments treated mouse diabetes models with mouse ES cells and got successful results (Soria et al., 2000). Later experiments used hematopoietic stem cells trans-differentiated into insulin producing cells (Beilhack et al., 2003; 2005) or reprogrammed adult mouse tissues to produce insulin (Zhou et

al., 2008; Alipio et al., 2010). With respect to human stem cells, human ES cells have been shown to be capable of being reprogrammed into insulin producing cells (Assady et al., 2001; Lumelsky et al., 2001; D'Amour, 2006), and human ES cells have been used to treat mouse models (Kroon et al., 2008), but human ES cells have not yet been used in human patients.

In one key early experiment with mouse ES cells, a team of scientists at the National Institute of Neurological Disorders and Stroke in Bethesda, Maryland was able to create "insulin-secreting structures similar to pancreatic islets" in mice with the use of mouse ES cells (Lumelsky et al., 2001). A later 2004 report used ES cells producing synthetic insulin to prove that the production of therapeutic insulin in the treated animals did not result from original pancreatic tissue. The insulin produced in the treated animals lacked the C-peptide, a short domain present in natural pre-insulin that separates the A and B chains of insulin (Hansson et al., 2004; Insulin C-Peptide, 2010). More research on this subject must be performed in order to determine if β cells have actually been produced.

The experiments performed with hematopoietic stem cells (HSCs) are interesting in that HSCs do not normally produce insulin, but scientists have determined that by injecting them into the right environment they can differentiate into insulin-producing cells. In one experiment performed by David Hess and others at the Robart's Research Institute in Ontario, the scientists injected bone marrow-derived HSCs in diabetic mice. The results showed that some insulin-positive cells were present in the mice, although the percentage of positive cells was low (Hess et al., 2003). This experiment showed that the repair and reproduction of pancreatic cells is possible using easily derived HSCs instead of ES cells. The possibilities for treating diabetes could be greatly facilitated by advancing stem cell research. This would help make lives easier for millions worldwide.

Stem Cell Treatment of Eye Injuries and Deficiencies

Even today, there is a wide variety of disorders and diseases that can cause degradation of retinal neurons, resulting in blindness and weakened eye sight. These eye disorders affect millions of patients, and can be caused by an array of factors. For example, there are currently more than 3.2 million people living with age-related macular degeneration (Ali & Sowden, n.d.). Age-related macular degeneration (AMD) is a disorder that disables central vision, leaving only peripheral vision. AMD is a disorder usually present in older patients; the risk greatly increases over the age of 75 according to the AMD alliance (Age Related Macular Degeneration, 2010). Besides AMD, an abundance of other disorders are associated with the loss of retinal neurons, including diabetic retinopathy, cataracts, and glaucoma, which together affect an estimated 6.2 million people worldwide. It is proposed that the use of stem cells could help treat these disorders by producing more necessary retinal neurons, such as light sensitive photoreceptors or retinal ganglion cell projection neurons, whose degeneration is the cause of blindness in many of these disorders. The use of stem cells could also be helpful in replenishing stem cells that are present on the surface of a patient's eye, which have been damaged via trauma or infection (Ali & Sowden, n.d.).

Epithelial stem cell reproduction is vital for the survival of a patient's eyesight. Similarly to other areas in the body lined by epithelial cells, the eye also possesses stem cells that are regenerated in the epithelial layer of the cornea. In the eye, these cells are referred to as limbal stem cells (Secker and Daniels, 2009). After an extreme case of eye trauma or infection, a deficiency in these limbal stem cells can result, and this inhibits the ability of the eye to form a healthy corneal surface. Although the first corneal transplant was performed by Eduard Zirm in 1905, this kind of transplant is not effective with eye disorders that result from the failure of the

epithelial layer of the eye (Shortt et al., 2011). In 1989, Dr. Kenyon and Tseng at the Eye Research Institute in Boston, MA conducted the first clinical trials performing limbal stem cell auto graft transplantation (Kenyon and Tseng, 1989). The study involved 26 cases of acute and chronic chemical injuries that caused a deficiency in limbal stem cells of one eye, or at least affected one eye much more than the other. Limbal stem cells were extracted from the patient's healthier eye and transplanted into the damaged eye. The results showed improvement in the patient's visual acuity and amount of rapid surface healing (Kenyon and Tseng, 1989). Later in 1994, Drs. Tsai and Tseng at the Chang Gung Medical College were able to successfully treat 13 of 16 patients affected with limbal epithelial stem cell deficiency disorders, by transplanting limbo-corneal grafts to the patient's eye from a relative or matched donor (Tsai and Tseng, 1994).

Later in 1997, Dr. Pellegrini and colleagues successfully grafted limbal stem cells from the healthy eye of a patient onto an eye that was injured by chemical burning (Pellegrini et al., 1997). In 2000, Dr. Tsai and his colleagues at Chang Gung Memorial Hospital were able to transplant cultured limbal epithelial cells from eye patients, and transplant them into the patient's unhealthy eye. The transplants lead to 83% of the patients making improvements with their eyesight, and their visual acuity improved from 20/112 to 20/45 (Tsai et al., 2000).

Taken together, these results have developed possible treatments for patients infected with ocular surface diseases or with limbal stem cell deficiencies. With further research and development, the use of limbal stem cells can make huge strides in the treatment of eye injuries and deficencies.

Stem Cell Treatment of Heart Disease

Today, coronary heart disease (CHD) is the leading cause of death for both men and women in the United States (Coronary Heart Disease, 2011). Heart disease is caused by the loss of heart muscle cells (cardiomyocytes) which help the heart pump blood through the arteries or is caused by a buildup of plaque in the arteries which reduces blood flow to tissues (Abdul et al., 2012). Either case makes it more difficult to supply blood and oxygen throughout the heart and body. CHD can cause life threatening complications, such as heart attacks, strokes, and pulmonary edema. CHD can be caused by a large array of things, such as genetics, diet, blood pressure, and age. However, if the muscles pumping blood through the heart and body could be replaced, this could help millions of heart disease victims (Coronary Heart Disease, 2011).

As discussed in Chapter-1, the heart uses cardiac stem cells (CSCs) to replace ageing or injured cardiac tissue, and ES cells have the potential to differentiate into cardiomyocytes. So perhaps these cells have therapeutic uses for treating CHD. In 1996, Dr. Klug at the Indiana University School of Medicine suggested an approach to producing cultures of cardiomyocytes by differentiating murine ES cells (Klug et al., 1996). In 2001, Dr. Kehat and colleagues were able to back up Klug's prior assumption showing that ES cells indeed have the potential to differentiate into cells with structural and functional properties of cardiomyocytes (Kehat et al., 2001). Kehat took human ES cells and applied several chemicals and growth factors to induce cardiac-like gene expression patterns to turn the cells into cardiomyocytes. The results showed that differentiated cells showed important functional properties also seen in early stage cardiomyocytes (Kehat et al., 2001). These differentiated ES cells might be used in future therapies for treating CHD, but have not yet been used in human patients.

With respect to using non-ES cells for treating patient CHD, several different types of adult stem cells have been tested, including cardiac stem cells (CSCs), skeletal myoblasts, and bone marrow stem cells (Baker, 2009). Dr. Britten at the University of Frankfurt, performed a clinical trial involving the transplantation of circulating blood progenitor cells into 28 heart attack patients having acute myocardial infarction (AMI), a common deteriorating heart condition. The data showed that the intracoronary infusion of adult peripheral HSCs beneficially "affects post infarction remodeling" in patients with AMI (Britten et al., 2003).

Skeletal myoblasts (SkM) are found in skeletal muscle, and are used by the body to help repair the muscle in the event of an injury. This makes SkMs a very good candidate for treating CHD (Durrani et al., 2010). There has been a large array of SkM studies performed, including a successful long-term rat skeletal muscle transplantation by Dr. Attar and colleagues in 2003 at the Hopital Europeen Georges Pomidou. They showed that after one year's time, the skeletal muscle cell transplantation was still successful (Attar et al., 2003). Dr. Siminak at the University of Medical Sciences in Poland performed a human clinical trial using autologous skeletal myoblasts for the treatment of AMI (Siminak et al., 2004). The skeletal myoblasts where injected into patients, who were observed for 12 months. Some complications were noted in several patients, but the overall improvement observed in cardiac function allowed the authors to conclude that the "observations justify further research" (Siminak et al, 2004).

With respect to using bone marrow stem cells to treat CHD, Dr. Orlic and colleagues of the New York Medical College, used rat models of myocardial infarction to show positive results of treating them with bone marrow cells (Orlic et al., 2001). They were able to show that newly formed myocardium occupied 68% of the infracted area of the heart (Orlic et al., 2001). But researchers had less success with human patients. In 2006, Dr. Lunde at Rikschospitalet

University Hospital performed a clinical trial with 50 patients with acute ST-elevation myocardial infarction. Unfortunately, when these patients were injected with bone marrow cells, they experienced no more myocardium repair than those patients injected with control cells (Lunde et al., 2006). In 2006, Dr. Schächinger at the Johann Wolfgang Goethe University performed a clinical trial with autologous progenitor cells taken from bone marrow. The trial was performed on 204 patients with AMI, half of the patients received an "intracoronary infusion of progenitor cells, while the other half received a placebo". Patients receiving the BMC showed significant improvement in the left ventricular contractile force compared to patients administered the placebo (Schächinger et al., 2006).

Chapter-2 Bibliography

Abdul M, Mozid SA, Mathur A (2012, May 19) Stem Cell Therapy For Heart Diseases. *British Medical Bulletin, 98:* 143-159.

Age Related Macular Degeneration (2010) Retrieved 7 1, 2012, from AMD Alliance International: http://www.amdalliance.org/information_overview.html

Ali RR, & Sowden JC (n.d.) Stem Cell Therapy For Blindness: New Developments and Implications for the Future. *Expert Review of Opthalmology, 6*(1): 1.

Alipio Z, Liao W, Roemer EJ, Waner M, Fink LM, Ward DC, Ma Y (2010) Reversal of hyperglycemia in diabetic mouse models using induced-pluripotent stem (iPS)-derived pancreatic β-like cells. *Proceedings of the National Academy of Sciences,* 107: 13426-13431.

Assady S, Maor G, Amit M, Itskovitz-Eldor J, Skorecki K, and Tzukerman M (2001) Insulin Production by Human Embryonic Stem Cells. *Diabetes,* 50: 1691-1697.

Attar NA, Carrion C, Ghostine S, Garcin I, Vilquin J-T, Hagege AA, et al. (2003) Long-term (1 year) functional and histological results of autologous skeletal muscle cells transplantation in rat. *Cardiovasc Res, 58*(1): 142-148.

Baker, Monya (2009) How to Fix a Broken Heart. *Nature,* 460: 18-19.

Beilhack GF, Scheffold YC, Weissman IL, et al (2003) Purified allogeneic hematopoietic stem cell transplantation blocks diabetes pathogenesis in NOD mice. *Diabetes,* 52: 59-68.

Beilhack GF, Landa RR, Masek MA, Shizuru JA (2005) Prevention of type 1 diabetes with major histocompatibility complex-compatible and nonmarrow ablative hematopoietic stem

cell transplants. *Diabetes*, 54: 1770-1779.

Bjorklund LM, Sanchez-Pernaute R, Chung S, Andersson T, Chen IYC, McNaught KSP, Brownell AL, Jenkins BG, Wahlestedt C, Kim KS, Isacson O (2002) Embryonic Stem Cells Develop Into Functional Dopaminergic Neurons After Transplantation in a Parkinson Rat Model. *Proceedings of the National Academy of Sciences USA*, 99(4): 2344-2349.

Bone Marrow Transplant (2012) Retrieved from Britannica Academic Edition: http://www.britannica.com/EBchecked/topic/72962/bone-marrow-transplant

Britten MB, Abolmaali ND, Assmus B, Lehmann R, Honold J, Schmitt J, Vogl TJ, Martin H, Schächinger V, Dimmeler S, Zeiher AM (2003) Infarct Remodeling After Intracoronary Progenitor Cell Treatment in Patients With Acute Myocardial Infarction. *Circulation*, 108: 2212-2218.

Coronary Heart Disease (2011, May 23) Retrieved July 2, 2012, from PubMed Health: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0004449/

D'Amour KA (2006) Production of pancreatic hormone–expressing endocrine cells from human embryonic stem cells. *Nature Biotechnology*, 24: 1392-1401.

Deeg J, Amylon M, & Harris RE (2001) Marrow Transplants From Unrelated Donors for Patients with Aplastic Anemia: Minimum Effective Dose of Total Body Irradiation. *Biology and Blood and Marrow Transplantation*, 7: 208-215.

Diabetes Facts. (2012, March 15). Retrieved June 15, 2012, from World Diabetes Foundation: http://www.worlddiabetesfoundation.org/composite-35.htm

Durrani S, Konoplyannikov M, Ashraf M, & Haider KH (2010, November) Skeletal Myoblasts for Cardiac Repair. *Regen Med, 5*(6): 919-932.

Ertelt, Steven (2009) Adult Stem Cell Research Reverses Effects of Parkinson's Disease in Human Trial. LifeNews.com, February 16, 2009. http://www.lifenews.com/bio2751.html

Frey MA, Guess C, Allison J, Kurtzberg J (2009) Umbilical Cord Stem Cell Transplantation. *Seminars in Oncology Nursing*, 25: 115-119.

Gonzalez-Ryan L, Van Syckle K, Coyne KD, Glover N (2000) Umbilical Cord Blood Banking: Procedural and Ethical concerns from this New Birth Option. *Pediatric Nursing*, 26: 105-110.

Hansson M, Tonning A, Frandsen U, Petri A, Rajagopal J, Englund MC, et al. (2004) Artificial Insulin Release from Differentiated Embryotic Stem Cells. *Diabetes*, 53: 2603-2609.

Hess D, Li L, Martin M, Sakano S, Hill D, Strutt B, et al. (2003) Bone Marrow-Derived Stem Cells Initate Pancreatic Regeneration. *Nature Biotechnology,* 21(1): 763-770.

Insulin C-Peptide (2010, April 19) Retrieved June 18, 2012, from Medline Plus: http://www.nlm.nih.gov/medlineplus/ency/article/003701.htm

Kehat I, Kenyagin-Karsenti D, Druckmann M, Segev H, Amit M, Gepstein A, Livne E, Binah O, Itskovitz-Eldor J, and Gepstein L (2001) Human Embryonic Stem Cells Can Differentiate Into Myocytes Portraying Cardiomyocytic Structural and Functional Properties. *Journal of Clinical Investigation,* 108: 407-414.

Kenyon K, & Tseng SC (1989, May) Limbal Autograft Transplatation for Ocular Surface Disorders. *Ophthalmology, 96*(5): 709-722.

Kim JH, M J, Auerbach, Rodriguez-Gomez JA, Velasco I, Gavin D, et al. (2002) Dopamine neurons derived from embryonic stem cells function in an animal model of Parkinson's disease. *Nature,* 418: 50-56.

Klug MG, Soonpaa MH, Koh GV, and Field LJ (1996) Genetically Selected Cardiomyocytes from Differentiating Embryonic Stem Cells Form Stable Intracardiac Grafts. *Journal of Clinical Investigation,* 98: 216-224.

Kroon E, Martinson LA, Kadoya K, Bang AG, Kelly OG, Eliazer S, et al. (2008) Pancreatic endoderm derived from human embryonic stem cells generates glucose-responsive insulin-secreting cells *in vivo*. *Nature Biotechnology,* 26: 443-452.

Leukemia (2012) Retrieved June 6, 2012, from Leukemia and Lymphoma Society: http://www.lls.org/#/diseaseinformation/leukemia/

Ludwig CD (2009) Leukemia. *MedSurg Nursing,* 18: 190-194.

Lumelsky N, Blondel O, Laeng P, Velasco I, Ravi R, & Mckay R (2001) Differentiation of Embryonic Stem Cells to Insulin-Secreting Structures Similar to Pancreatic Islets. *Science ,* 292: 1389-1394.

Lunde K, Solheim S, Aakhus S, Arnesen H, et al. (2006) Intracoronary Injection of Mononuclear Bone Marrow Cells in Acute Myocardial Infarction. *The New England Journal of Medicine,* 355: 1199-1209.

May TS (2002) Transplantation of Embryotic Stem Cells in Parkinson's Disease. *The Lancet Neurology,* 1(1): 6.

Mayer J, Prospisil Z, & Koristek Z (2003) Mathematical Model of Peripheral Blood Stem Cell Harvest Kinetics. *Bone Marrow Transplantation*, 32: 749-757.

McCulloch EA, & Till JE (2005) Perspectives on the Properties of Stem Cells. *Nature Medicine,* 11: 1026-1028.

Orlic D, Kajstura J, Chimenti S, Jakoniuk I, Anderson SM, Li B, Pickel J, McKay R, Nadal-Ginard B, Bodine DM, Leri A, and Anversa P (2001) Bone Marrow Cells Regenerate Infarcted Myocardium. *Nature*, 410: 701–705

Pellegrini G, Traverso C, Franzi A, Zingirian M, Cancedda R, & Luca MD (1997, April 5) Long-term restoration of damaged corneal surfaces with autologous cultivated corneal epithelium. *Lancet, 349:* 990-993.

Perrier AL, Tabar V, Barberi T, et al. (2004) Derivation of midbrain dopamine neurons from human embryonic stem cells. *Proc Natl Acad Sci USA,* 101: 12543-12548.

Raju TN (2000) The Nobel Chronicles. 1990: Joseph Edward Murray (b 1919) and E Donnall Thomas (b 1920). *Lancet,* 355: 1282.

Rosenbeck LL, Srivastava S, & Kiel PJ (2010) Peripheral Blood Stem cell Mobilization Tactics. *Annals of Pharmacotherapy*, 44: 107-116.

Ryan C (2004) Stem Cell Therapy for Parkinson's. BBC News. http://news.bbc.co.uk/1/hi/health/3853791.stm

Schächinger V, Erbs S, Elsässer A, Haberbosch W, Hambrecht R, et al. (2006) Intracoronary Bone Marrow–Derived Progenitor Cells in Acute Myocardial Infarction. *The New England Journal of Medicine*, 355: 1210-1221.

Secker, G A., & Daniels, J T. (2009). Limbal Epithelial Stem Cells of the Cornea. Retrieved August 1, 2012, from Stembook.org: http://www.stembook.org/node/588

Shortt AJ, Tuft SJ, & Daniels JT (2011, August 14) Corneal Stem Cells in the Eye Clinic. *British Medical Bulletin, 100*(1): 209-225.

Siminiak T, Kalawski R, Fiszer D, Jerzykowska O, Rzeźniczak J, Rozwadowska N, Kurpisz M (2004) Autologous skeletal myoblast transplantation for the treatment of post-infarction myocardial injury: Phase I clinical study with 12 months of follow-up. *American Heart Journal,* 148: 531-537.

Soria B, Roche E, Berna G, Leon-Quinto T, Reig JA, Martin F (2000) Insulin-secreting cells derived from embryonic stem cells normalize glycemia in streptozotocin-induced diabetic mice. *Diabetes,* 49: 157-162.

Studer L, Tabar V, and Mckay RG (1998) Transplantation of Expanded Mensencephalic Precursors Leads to Recovery in Parkinsonian Rats. *Nature Neuroscience,* 1: 290-295.

Takahashi J (2007) Stem Cell Therapy for Parkinson's Disease. *Expert Review of Neurotherapeutics,* 7: 667.

Thomas ED, Lochte HL, Lu WC, et al. (1957) Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy. *New England Journal of Medicine,* 257: 496-496.

Tsai RJ, Tseng SC (1994, September 13). Human allograft limbal transplantation for corneal surface reconstruction. *Cornea, 13*(5): 389-400.

Tsai R, Li L, & Chen J (2000, July 13) Reconstruction of damaged corneas by transplantation of autologous limbal epithelial cells. *New England Journal of Medicine, 343*(2): 86-93.

Types of Bone Marrow Transplants (2009) Retrieved June 2012, from Cleveland Clinic: http://my.clevelandclinic.org/services/bone_marrow_transplant/types.aspx

Wagner JE, & Gluckman E (2010) Umbilical Cord Blood Transplantation: The First 20 Years. *Seminars in Hematology ,* 47 (1): 3-12.

Yang J-R, Lin Y-T, & Liao C-H (2011) Application of Embryotic Stem Cells on Parkinson's Disease Therapy. *Genomic Medicine, Biomarkers, and Health Sciences* , 3 (1): 17-26.

Zhou Q, Brown J, Kanarek A, Rajagopal J, Melton DA (2008) *In Vivo* Reprogramming of Adult Pancreatic Exocrine Cells to β-Cells. *Nature,* 455: 627-632.

Zieve D, & Eltz DR (2011a, September 26). *Parkinson's Disease*. Retrieved June 2012, 15, from PubMed Health: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001762/

Zieve D, & Eltz DR (2011b, August 31) *Diabetes*. Retrieved June 15, 2012, from A.D.A.M: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002194/

Chapter-3: Stem Cell Ethics

Sean Kelly

Ethical standards play a major role in society's scientific progression. Depending on the specific technology, ethical debates (and the ensuing legislation) can stimulate technology (as with the federal support of adult stem cell research), or it can hinder technology (as with the prohibition of federal support for embryonic stem cell research during the Bush administration). The moral conflict is never more apparent than in the current stem cell debates. The purpose of this chapter is to discuss the ethics of the stem cell debate, providing input from the five major world religions. The author also provides his own assessment and conclusions of the debate at the end of the chapter.

Framing the Stem Cell Debate

When discussing the controversy of stem cells, the main concern involves the research of embryonic stem (ES) cells, and the destruction of the embryo that results from their derivation. As discussed in Chapter-1, ES cells are derived from the inner cell mass of a 5-day old blastocyst embryo prepared by *in vitro* fertilization (IVF). The 5-day old embryo is destroyed when the ES cells are isolated, so the debate focuses on the rights or status of the 5-day old embryo and when personhood begins. If one believes that personhood begins at conception, then a 5-day old embryo is a person, and its destruction is 'murder'. However, if one believes that personhood begins at day-40 or at birth, then a 5-day old embryo is only a *potential* person, not a fully realized person. IVF embryos can only become a baby if they are implanted into a uterus, they cannot grow to be an adult without the aid of pregnancy.

It may surprise some people to learn that the embryo debate is not new. The embryo debate has raged since 1978 with the birth of Louise Brown, the world's first test tube baby (BBC News, 1978). So, the embryo debate has origins with the IVF procedure itself. IVF procedures do not always work, so extra embryos are prepared at the time of gamete (egg and sperm) donations. Once the family has enough children, the remaining embryos are considered 'extra', and are either discarded or are donated for research purposes. The debate about what to do with the extra IVF embryos, whether to create them in the first place, or to try to save lives with ES cells, is central to the stem cell debate. So, the debate focuses on a discussion of the *benefits* of the stem cell research (discussed in Chapter-2) versus the *rights* of the embryo. Is it correct to take the 'life' of an embryo, while trying to save the life of a person already born? The benefits to society of stem cells is constantly expanding, so the debate has evolved from discussing the potential of stem cells to save lives, to how many different diseases can stem cells potentially treat.

Although ES cell research is at the forefront of the stem cell debate, new types of stem cells are being discovered all the time, and these cells factor into the debate. For example, iPS cells appear to be pluripotent yet they do not destroy an embryo to derive them. And parthenote embryos cannot form a baby, but can be used to derive new ES cell lines. What is the status of these new types of stem cells?

A good place to start when considering the beginning of human life and personhood is the five major world religions. These religions all have their own beliefs, sacred texts, and laws that guide their followers in making moral decisions. The five major world religions are: Christianity, Judaism, Islam, Hinduism, and Buddhism. Although these religions have some

points in common, for example they all strongly approve the use of *adult* stem cells, each has their own views of when personhood begins, and the value placed on healing others.

Christianity and Stem Cells

The Christian view on this debate, is complex as expected for a major world religion. Catholics have their own stance, which may differ from other Christian religions such as Methodists or Baptists. When interpreted directly from the Holy Bible, the general view appears to be against the use of embryos or ES cells for research, based on the high value placed on all life as stressed in the Old Testament. The *Didache*, a Second Century writing of the teaching of the Twelve Apostles, speaks against abortion of all kinds (Fleischmann, 2001). But on the other hand, medieval Christians, with the exception of Catholics, generally considered that an embryo acquired a soul only after it took a recognizable human shape (well after day-5). So, abortion was a crime, but it was not equal to murder. Although a high regard is placed on life in the womb, IVF embryos used to derive ES cells do not reside in the womb.

Catholicism

Catholicism is one of the religions that strongly disproves of the use of human embryos for research (American Catholic Organization, 2006). Several different Popes as leader of the church have been quoted as saying that life begins at conception and that embryo research is wrong (Pope John Paul, 2001; Pope Benedict, 2008). In 1996, U.S. Catholic bishops approved a statement that considers embryo research to be 'gravely immoral' and unnecessary (O'Brien, 1996). In June of 1996, the U.S. bishops voted 191-1 in favor of the document: "On Embryonic Stem-Cell Research: A Statement of the U.S. Conference of Catholic Bishops" (O'Brien, 1996).

This document was often referenced, and laid out the three main reasons the church opposed embryo research: 1) the possible benefits do not outweigh the destruction of embryos, 2) what is being destroyed is indeed human life or at least a being with human rights, and 3) the opposition extends to killing leftover embryos created by *in vitro* fertilization. With respect to point-1, the document states that "no commitment for a hoped-for 'greater good' can erase or diminish the wrong of directly taking innocent life here and now". It also goes on to say that "the false assumption that a good end can justify direct killing has been the source of much evil in our world" (Malloy, 2008). From the Catholic perspective, this clearly refutes the reason that the benefits will outweigh the killing of human embryos. With respect to point-2, the document states that these embryos contain all of the human genes and is deserving of all rights and dignity given to the human race (Malloy, 2008). The document also takes this refutation a step further by saying "If fundamental rights such as the right to life are based on abilities or qualities that can appear or disappear, grow or diminish, and be greater or lesser in different human beings, then there are no inherent human rights, no true human equality, only privileges for the strong" (O'Brien, 1996). With respect to point-3, when considering the fact that the leftover embryos from IVF clinics might be used for testing because they will end up dying regardless, the document states "Ultimately each of us will die, but that gives no one the right to kill us. Our society does not permit lethal experiments on terminally ill patients or on condemned prisoners with the pretext that they will soon die anyway. Likewise, the fact that an embryonic human being is at risk of being abandoned by his or her parents gives no individual or government a right to directly kill that human being first" (Malloy, 2008).

Thus, with respect to embryo and ES cell research, it is clear what is expected of Catholics and how they are to respond to such an ethical controversy. On the other hand, the

Catholic Church fully supports research involving *adult* stem cells (Pope Benedict, 2008). Deriving stem cells from an adult does not affect the patient in a negative fashion and does not interrupt the process of life, so therefore the Catholics completely support it.

Non-Catholic Christians

With respect to Christians other than Catholics, their stance varies depending on the sect. For example, the Book of Resolutions of the United Methodist Church indicates that Methodists have no objections to conducting research on adult stem cells or those derived from umbilical cords, but believe embryos deserve reverence (United Methodist Church, 2004). However, they do not believe that the embryos deserve as much reverence as an adult life. Methodists recommend the following guidelines: during IVF, clinicians and couples should be required to determine how many eggs to fertilize and implant on a case by case basis, there should be a limitation of creating one embryo for implantation at a time, and finally a set of standards needs to be put together regarding the proper disposition of excess embryos (United Methodist Church, 2004). The use of existing embryos for research after the couple is done having children is accepted in the Methodist religion. This is dissimilar to what Catholics believe. Other non-Catholic Christian denominations appear to also support embryo research with some restrictions (Faithful Progressive, 2005).

Hinduism and Stem Cells

The Hindu Vedas, the religion's Holy Scripture, proclaims that all life is sacred, even plant and animal life (Bhanot, 2008). This 'respect for life' and "ahimsa" (non-violence) are essential Hindu beliefs. All living things are God's creations in the Hindu point of view.

However, Hindu's are strong believers in the law of nature. As humans, the use of plants and animals to survive is a necessity. This life works by taking the life of a lower form of evolution and using it for survival. Hindu's separate life into three levels: plants, animals, and humans, in this order of increasing consciousness. In Hinduism there is also the fundamental belief that the soul passes through many species (as many as 8.4 million according to one ancient scripture) before it reaches the highest level of consciousness, human. They believe that human birth can bring about salvation from the repeated cycles of rebirth, and finally allow one to come face to face with God. As a human being, the highest achievement has been met within reincarnation. Since medical research tries to increase human survival, and adult humans are closer to God than embryos, Hindus generally support medical research, as it increases life at the highest level of reincarnation. However, due to their respect for all life and non-violence, Hindus do not take a strong stand in favor of embryo research (Bhanot, 2008).

Islam and Stem Cells

The sacred book the Quran, and the Shari'ah or Islamic law interpreted from the sacred book, set the ethical standards for Islam. With respect to the embryo debate, the Shari'ah mentions that there needs to be a clear distinction made between *actual* life and *potential* life (Siddiqi, 2002; Weckerly, 2002). Thus, there is a difference between a fertilized ovum in a petri dish, and a fertilized ovum in a woman's womb. Islam believes that the embryo has the potential to grow into a human, but is not yet a human. Islamic officials and followers also believe the embryo does not acquire a soul until 120 days after fertilization (Siddiqi, 2002), and there is a clear distinction between the early stage and the late stage of pregnancy. For example, if someone attacks a pregnant woman and this leads to the death of her baby in the early stage (first

40 days), then this person's punishment would be less than if the attack occurred late in pregnancy. Considering these concepts, Islam is generally in favor of embryo research. Outside of the womb, this form of life cannot become a human or even survive. The embryo is not an independent life form, so the Islamic people see no major ethical issues with using spare embryos for research.

Muslim's do however understand the ways to obtain embryos for research can be corrupt. Examples of this include infertile patients being forced to go through extra ovulation cycles, paying money for donations of embryos, or even using embryos without the consent of the donor (Siddiqi, 2002). They know that laws need to be set to avoid these serious ethical issues, specifically clarifying the difference between leftover embryos, and embryos created solely for research. Islamic people also support studies involving adult stem cells.

Judaism and Stem Cells

The Torah, the Jewish sacred text, charges Jews to strive to grasp new knowledge, and pursue new technologies to improve life (Eisenberg, 2006). A very strong value is placed on human life in this religion, which places a priority on the continuation of research concerning human healing and stem cells. Judaism places strong emphasis on life beginning forty days after conception. Jews take these forty days of gestation and consider the embryo to be "mayim b'alma", or "mere water" (Eisenberg, 2006). Some Rabbi's believe this mere water is not considered to be human, and therefore destruction of the embryo in this stage is not forbidden by Jewish law. However, after forty days the Jews strongly uphold the belief that no life should be taken to save another life (Jakobovits, 2006). As for the IVF embryo, they believe it has no real potential of developing into a human, so there is no opposition to use these spare embryos for

research as opposed to disposing of them. Jews feel that it is very hard to justify prohibiting the use of possible life saving cells if they are just going to be discarded and killed anyways. This applies to aborted fetuses and spare embryos from *in vitro* fertilization clinics.

In addition, Jews also strongly believe that screening embryos that are to be used in clinical practice is necessary to prevent later genetic diseases. For example if both the egg and the sperm are carriers of Tay Sachs disease (a hereditary disease that can lead to severe muscle defects, delays in learning, blindness deafness, and death) then the embryo can be discarded. This sets the framework for the debate for Judaism, if an embryo can be killed by discarding it for being defective, it can also be used to try to save lives.

Buddhism and Stem Cells

Buddhism is strongly influenced by the Buddha's teachings, *dhamma,* as well as the sacred texts such as the Theravada (Keown, 2004). The Buddhist religion provides moral advice, does not have one God, and does not morally dominate (Promta, 2004). The *dhamma* is interpreted by Buddhist's as natural things and natural laws, such as physics, chemistry and biology (Promta, 2004). Followers believe the universe was naturally given, and do not seek to find answers concerning the origin or end of it. The most critical aspect of the point of view of the Buddhist religion with respect to embryo research lies in human rights. They separate rights into two main categories; right to life, and right to property. When considering property, violation of the rights of a minority is accepted when the majority will indeed benefit. However, in terms of life, no sway in majority can make killing life ethical, because life is not transferrable (Promta, 2004). Buddhist's believe that at the moment of conception, the embryo is human and is immediately granted the same rights an adult would have.

The Buddhist religion places high importance on the central virtues of knowledge (*pranja*), compassion (*karua*), and on bettering the medical field (Keown, 2004). There is a high priority on developing treatments to eliminate human suffering. In contrast to this, Buddhists also see the principle of no-harm or *ahisma* as having superiority over any medical or scientific practice that harms or destroys life; the destruction of human embryos is morally impermissible. This belief covers the use of spare IVF embryos, regardless of intent. The Buddhist views of using aborted tissues conflict, as some consider the aborted fetus deceased, but abortion itself is immoral. The general Buddhist stance against embryo and ES cell research is surprising, given the research breakthroughs that have occurred Korea where the population is mostly Buddhist.

Ethics of iPS Cells

As discussed in Chapter-1, induced pluripotent stem (iPS) cells are adult skin fibroblast cells directly reprogrammed to a pluripotent-like state by adding two to four transcription factors to induce the reprogramming. No embryos are used or killed in this process, and they do not risk the health of women egg donors (Cohen and Brandhorst, 2008). Although the initial four factor programming included *c-Myc*, that factor tended to induce tumors, so it has now been left out of the process, and scientists have also developed procedures for omitting the retroviral vectors and just directly treat with the transcription factors (Reprogramming, 2009). The true potency of these cells is still being investigated, but if they are shown to be pluripotent they could perhaps take the place of embryo-derived ES cells for therapies. Other scientists worry that iPS cells could become totipotent (capable of forming an entire organism). If so, they would have the same ethical concerns as normal embryos. In recent research, totipotency has not been a

problem because iPS cells have not been able to form extra-embryonic tissues like totipotent cells (Brind'Amour, 2009).

Parthenote Ethics

Parthenogenesis is mode of asexual reproduction used by some species of lower organisms, for example to make worker bees and ants. In this process, an egg is stimulated to begin dividing without the input from sperm. Parthenogenesis does not occur naturally in mammals, but scientists have devised an artificial method for stimulating egg division using electric current or chemicals to trick the egg into dividing without losing one set of chromosomes as an egg normally does. If the egg can divide to the blastula stage (100 cells) sometimes ES cells can be derived. Parthenote embryos have been derived from monkey eggs (Mitalipov et al., 2001) and human eggs (Brevini and Gandolfi, 2007). The mammalian parthenote embryos cannot divide beyond the blastocyst stage, so cannot produce a baby.

So the debate focuses on the status of parthenote embryos. Although mammalian parthenotes cannot develop into a human, some scientists believe by killing these "virgin birth" embryos human dignity is still being disrespected; they believe that the parthenotes show human like characteristics for several days, and this to them is enough to say such research is ethically wrong. However, further research needs to be conducted to understand the entirety of this process, and to determine the true biological potential of these embryos; after all, the debate would alter considerably tomorrow if a scientist figured out a way to make parthenote embryos develop to full human beings inside a uterus, so the debate would then become similar to that for excess IVF embryos. Until the true developmental potential of mammalian parthenote embryos is known, the debate cannot be settled. So, perhaps more research needs to be done in this area

(Brugger, 2011). An oocyte or woman's egg is not an embryo; however the oocyte divides after electrical and chemical stimulation, mimicking a human embryo. Also, the controversy of "virgin birth" is a big one for Christianity. This is how the savior, Jesus Christ, was perceived to have been born. Parthenogenesis does not involve a male partner, forming many ethical questions from this religion.

Author's Chapter-3 Conclusion

After completing the research for this chapter, and viewing the various religious stances on embryos and stem cells, the author of this chapter has a few personal conclusions to make. I believe that deriving embryonic stem (ES) cells from embryos to prepare ES cell lines is acceptable, with limitations. I agree with the current Obama administration's policies that the human embryos should come only from the *excess* embryos of reproductive IVF clinics, and only with donor consent. IVF needs to be tightly regulated, with clinicians and patients working together to determine a reasonable number of embryos to create to avoid a large excess. No pressure should be placed on the family to create more embryos than necessary. I believe the embryos should be treated with respect, and that a 5-day old embryo with *potential* life (if implanted into a uterus) not yet a person, can be used for research, especially if it is about to be discarded. Discarding an already created embryo is killing potential life, without any way to produce any positives from the act for the future. The author believes no embryos should be created solely for research; this is unethical, and could lead to individuals undergoing risky egg donation procedures solely for the money offered. With respect to unfertilized parthenote embryos, the author does not consider them to have the same status as a fertilized embryo, so they can be used to derive new ES cell lines. Although some religions might associate this type

of artificial 'virgin birth' with the Virgin Mary, the author who is Roman Catholic, does not associate parthenogenesis with "virgin birth". I consider parthenogenesis as scientific birth; no miracles take place in the laboratory during this process, just scientific reactions.

Abortion is only tangentially related to the stem cell debate, as aborted fetuses are not used in stem cell research. But after discussing the various religious stances on embryos, and given my background as a Roman Catholic, I believe abortion is only acceptable under the circumstance of rape. In this case I believe the woman's rights were completely violated, so she now has the right to decide how she wishes to deal with the embryo. If a decision to abort is made, the fetus should be aborted as early as possible in the first trimester, and with donor consent the tissue can be provided for research. The author believes that abortion performed to correct a fertility mistake when the parents don't want the child is murder. If a miscarriage occurs naturally, the fetus should only be used for research with the mother's consent.

With respect to adult stem cells (ASCs), although I am generally in favor of working with embryos, I believe ASCs should be used whenever possible if that specific disease can be treated with ASCs. There are only minimal ethical issues with ASCs, such as making sure they are used for medical purposes to save lives, and all of the major religions support their use under those conditions. The use of iPS cells also has my full support, so long as the newer scientific protocols are used (with only two transcription factors without the *c-Myc* oncogene) that greatly reduce the chance of cancer formation from the transplanted cells.

Religion, ethics, and science will always come into play when discussing the fate of embryos and stem cells. The stem cell controversy began with the advent of IVF procedures and deciding the fate of excess embryos, and will continue to be one of the major bio-ethical debates

of our era. As is the case for any controversial science, its use must be tightly regulated by laws.

This is the subject of the next chapter.

Chapter-3 References

American Catholic Organization (2006) U.S. Bishops Protest Embryo Stem-cell Research. http://www.americancatholic.org/News/StemCell/bishops_stemcell.asp

Bahnot, Anil (2008) The Ethics of Stem Cell Research: A Hindu View. *Bio News*. 17 Oct. 2008. http://www.bionews.org.uk/page_38022.asp

Baylis, Francoise (2008) ES Cells and iPS Cells: A Distinction With a Difference. *Bioethics Forum: Diverse Commentary on Issues in Bioethics*. The Hastings Center, 3 Apr. 2008. http://www.thehastingscenter.org/Bioethicsforum/Post.aspx?id=730

BBC News (1978) First Test Tube Baby Born. http://news.bbc.co.uk/onthisday/hi/dates/stories/july/25/newsid_2499000/2499411.stm

Brevini X, Gandolfi F (2007) Parthenotes as a Source of Embryonic Stem Cells. http://www.blackwell-synergy.com/doi/pdf/10.1111/j.1365-2184.2008.00485.x

Brind'Amour, Katherine (2009) Ethics of Induced Pluripotent Stem Cells. *Suite101.com*. 24 May 2009. http://www.suite101.com/content/ethics-of-induced-pluripotent-stem-cells-a75390

Brugger EC (2011) Stem Cells and Parthenogenesis: Are Parthenotes Human Embryos? Lifeissues.net. http://www.lifeissues.net/writers/bru/bru_35parthenogenesis.html

Cohen C, and Brandhorst B (2008) Getting Clear on the Ethics of iPS Cells. *Bioethics Forum: Diverse Commentary on Issues in Bioethics*. 2 Jan. 2008. http://www.thehastingscenter.org/Bioethicsforum/Post.aspx?id=710

Eisenberg, Daniel (2006) Stem Cell Research in Jewish Law. *Jewish Law Articles*. Ira Kasden. Jewish Law. http://www.jlaw.com/Articles/stemcellres.html

Faithful Progressive (2005) Why Christians Should Support Stem Cell Research. *Christian Alliance for Progress: The Movement to Reclaim Christianity and Transform American Politics.* 27 May 2005. http://blog01.kintera.com/christianalliance/archives/2005/05/why_christians.html

Fazzetto, Giovanni (2004) Embryos, Cells and God. *EMBO Reports*, 5: 553-55. http://www.nature.com/embor/journal/v5/n6/full/7400175.html

Fleischmann J (2001) The Christian View on Embryonic Stem Cell Research: The Guidance of Holy Scripture. http://resqrev.com/Embryonicb.pdf

Griffin, Stan (2010) Five Major World Religions. Workers for Jesus. http://www.workersforjesus.com/five.htm

Jakobovits, Yoel (2006) Judaism and Stem Cell Research. Torah.org. Project Genesis, Inc. http://www.torah.org/features/secondlook/stemcell.html

Keown, Damien (2004) 'No Harm' Applies to Stem Cell Embryos: One Buddhist's Perspective. *Belief Net*. http://www.beliefnet.com/story/143/story_14399_1.html

Malloy DJ (2008) On Embryonic Stem Cell Research. http://old.usccb.org/prolife/issues/bioethic/bishopsESCRstmt.pdf

Mannoia, Kristyn (2004) An Evaluation of Three Religious Perspectives on Stem Cell Research. *Asa3*. Sept. 2004. Student and Early Career Scientists Corner. http://www.asa3.org/aSA/PSCF/2004/PSCF9-04Mannoia.pdf

Mitalipov SM, Nusser KD, and Wolf DP (2001) Parthenogenetic Activation of Rhesus Monkey Oocytes and Reconstructed Embryos. *Biol Reprod*, 65: 253-259. http://www.biolreprod.org/content/65/1/253.full.pdf+html

O'Brien, Nancy F (1996) Stem Cell Research and The Catholic Church. AmericanCatholic.org. St. Anthony Messenger Press, 1996. http://www.americancatholic.org/news/stemcell

Pope Benedict XVI (2008) Benedict endorses adult stem-cell research as respecting human life. Catholic Online. http://www.catholic.org/international/international_story.php?id=21301

Pope John Paul II (2001, Jan 23) A Crisis of Values. *CNN.Com.* http://archives.cnn.com/2001/WORLD/europe/07/23/bush.pope/

Promta S (2004) *Human Cloning and Embryonic Stem Cell Research - A View From Therav*. Bangkok, Thailand: Chulalongkorn University. Retrieved Oct 15, 2007 from http://www.stc.arts.chula.ac.th/Cloning%20and%20Stem%20Cell-Buddhist.pdf

Reprogramming Offers Hope of Safer Stem Cells (2009) *NewScientist.* http://www.newscientist.com/article/dn17008-reprogramming-offers-hope-of-safer-stem-cells.html

Siddiqi, Muzammil (2002) An Islamic Perspective on Stem Cell Research. *IslamiCity.com*. 27 Feb. 2002. http://www.islamicity.com/articles/Articles.asp?ref=IC0202-404

United Methodist Church (2004) *Ethics of Embryonic Stem Cell Research.* http://archives.umc.org/interior.asp?ptid=4&mid=6560

Weckerly M (2002) The Islamic View on Stem Cell Research. *Rutgers Journal of Law and Religion.* http://org.law.rutgers.edu/publications/law-religion/new_devs/RJLR_ND_56.pdf

Chapter-4: Stem Cell Legalities

Michael Boyd

In 1957, Dr. Thomas at the University of Washington performed the first clinical bone marrow transplant (Thomas et al., 1957). Since this first successful procedure, the study of stem cells for treatment of diseases has been a large focus of the world's medical research community. However, there are several ethical factors which limit many forms of stem cell research; for example, the use of human embryos for harvesting stem cells. Embryonic stem (ES) cells are obtained from excess 5-day old embryos from *in vitro* fertilization (IVF) clinics. The ES cell debate focuses on the status of excess IVF embryos. Accordingly, several laws have been established that do not allow for federal funding of ES cell research, although privately funded stem cell institutions are allowed. In the United States specifically, laws which limit and regulate stem cell research are strongly reflective of the executive branch's position on the subject. This chapter will begin with a discussion of United States federal laws, specific to several recent executive branch administrations, followed by a discussion of laws specific to various U.S. states, and end with a discussion of international stem cell laws.

A gross public misconception is that the stem cell debate is new. Ethical discussion of excess IVF embryos initiated with the birth of the world's first test tube baby in 1978, Louise Brown. Louise was created by *in vitro* fertilization; an egg from her mother was fertilized with sperm from her father in the laboratory (BBC News, 1978). The zygote was grown to the blastocyst stage, and then implanted into Mrs. Brown. With the advent of IVF, debates ensued about what to do with the remaining excess human embryos not used for reproduction. A supply of unusable 5-day post-fertilization embryos became available for research, allowing for a rise in the human embryonic stem (ES) cell supply. For the first time in history, scientists had access to

embryos that could be used to isolate ES cells for research. Earlier, in 1973, following the outcome of the landmark *Roe v. Wade* legal case (which ruled that federal regulation of abortion is unconstitutional), scientists were permitted access to aborted fetal tissue. The moral issues associated with the use of discarded aborted fetal tissue in research raised a lot of questions, creating an anti-abortion movement, which greatly opposed fetal research (Wertz, 2002). The public often confuses aborted fetal tissue with 5-day old IVF embryos, the latter are a small cluster of cells, referred to as a blastocyst. Embryos can be created by IVF and grown only for about 5-10 days before requiring implantation into a uterus. The fetal stage represents a much later stage of development, and requires uterine implantation. Although scientists briefly used aborted fetal tissue implants to treat Parkinson's patients (Madrazo et al., 1988), the use of fetal tissues in medicine was far more controversial than using excess IVF embryos, and the use of fetal tissues in research was outlawed. The ES cell debate focuses on the status of 5-day old IVF embryos, not on aborted tissues.

Early Fetal and Embryo Legalities (1973-1992)

In January of 1973, the *Roe v. Wade* case U.S. Supreme Court ruled in *Roe v. Wade* that a woman's right to privacy under the 14th Amendment extended to her decision to have an abortion, but her right must be balanced against the state's right to protect prenatal life and protect a woman's health. Initially, the right for a woman to have an abortion was limited to the first two trimesters (ROE v. Wade, 410 U.S. 113, 1973). This landmark court case disallowed many state and federal blocks on abortions. As a result of the case, in 1973, the Department of Health, Education, and Welfare (DHEW, now known as the DHHS) was established to oversee medical research in the U.S. This agency, while considering the availability of fetal tissue

resulting from *Roe v Wade*, and the availability of embryo tissue resulting from the then new IVF procedures, immediately placed a moratorium on all human embryo research, preventing further research until a set of ethical rules could be set in place. In 1974, the United States Congress placed its own moratorium on all federally funded research of embryos or embryo tissue, which included "IVF, infertility, and prenatal diagnosis" types of research (Wertz, 2002). Human embryo research was still legal, but only if funded by private research labs. Furthermore, in the December of 1974, Congress also established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research to create and mandate ethical guidelines for embryonic research, and to create general guidelines for conduct of biomedical and behavioral research involving humans (The National Commission….1975). Throughout the 1980's, there was very little support by the United States government for federally funding of ES cell research. A large portion of congress did not support such research, fearing it could lead to an increase in paid donors of egg and sperm.

In March of 1988, the National Institute of Health (NIH) established the Human Fetal Tissue Transplantation Research Panel. Members from this board included scientists currently working with stem cell research, such as Dr. Lars Olson and Dr. Eugene Redmond. Dr. Olson was working with Parkinson-like disease in monkeys at Yale University, and Dr. Lars Olson was also experimenting Parkinson's treatments at the Karolinska Institute in Stockholm. Both of these scientists expressed their interest in the use of fetal tissue and embryonic stem cells for medical applications. The NIH panel recommended that the research of fetal tissue should not be stopped, but supported (Barnes and Stevenson, 1989). However, the compelling evidence presented by the panel was not effective, and in November of 1989 the DHHS placed a moratorium on federal funding of ES cell research. When Congress voted to override it in 1990,

President George Bush senior vetoed the attempt. Accordingly, from 1975 to 1992, there was no federally funded ES cell research, so ES cell research remained in the private sector, which severely dampened the potential for medical advances resulting from ES cell research (Wertz, 2002).

Clinton Administration (1993-2001)

Former President Bill Clinton was inducted into office in January of 1993, and made it his executive action to retract several previous restrictions on medical research. The newly elected president abolished the moratorium on federal funding of fetal tissue research (The Clinton Presidency, 2012). Additionally, President Clinton also established the National Institutes of Health (NIH) Embryo Research Panel, which consisted of a panel of expert scientists in the medical field given the task of determining whether research on fetal tissue or embryos should receive federal funding. In 1994, the NIH panel released their recommendations, which strongly supported the federal funding of ES cell research, but not fetal tissue. One particular recommendation suggested as a source of ES cells discarded IVF embryos, donated by couples in reproductive IVF programs (Stith-Coleman, 1998). However, President Clinton rejected the NIH panel's recommendation to allow the production of embryos *in vitro* solely for research purposes, leaving only donated IVF embryos from reproductive clinics as a federally funded source of embryos (Dunn, 2005).

In 1994, the view of congress shifted when the Republican Party retook control of the Senate and House of Representatives, eventually causing a reduction of ES cell research in the United States. In 1995, a new amendment was issued from the United States Congress which abolished federal funding of embryonic stem cell research. The Dickey-Wicker Amendment

eradicated the availability of federal funding for "creating, destroying, or knowingly injuring human embryos" for any scientific research (Kearl, 2010). Senate Representatives Jay Dickey of Arkansas and Roger Wicker of Mississippi authored the Amendment. The amendment was passed as an appropriations bill, which stipulated that it would be reviewed and voted on each year by the House of Representatives (Kiessling, 2010).

In 1998, James Thomson of the University of Wisconsin without the use of federal funding successfully isolated human embryonic stem cells from human IVF blastocysts, creating the world's first human ES cell line (Thomson et al., 1998). Later, in 1999, Harriet Rabb declared that since human ES cells are "not human embryos within the statutory definition" that only the *process* of isolating them broke the Dickey-Wicker Amendment. So, legally the NIH now had the option to federally fund any institution that acquired ES cells from privately funded institutions. In September of 1999, the National Bioethics Advisory Commission released its guidelines, which suggested allowing federal money to study human IVF embryos, but the commission did not support the creation of embryos solely for research (Sharpiro et al., 1999). Near the end of President Clinton's administration, an initial federal funding of ES cell research, coupled by a broader acceptance of the use of ES cells, allowed some expansion of human ES cell research.

The Bush Administration and Stem Cells (2001-2009)

Former President George W. Bush took office in January of 2001, and soon enacted several policy changes which significantly decreased the availability of human ES cells for medical research (Beschloss & Sidey, 2009). On August 9th 2001, President George W. Bush addressed the nation with his new policy severely limiting federal funding for human embryo

and fetus tissue research. In his address to the nation, President George W. Bush stated that he found the creation of human embryos for the sole use of experimentation "deeply troubling", and enacted several new policies for the protection of human embryos (Bush, 2001). The new policies restricted the availability of federal funding for ES cell research with a harsh new stipulation. In order to receive federal funding for continued research, the ES cell line used for research had to be derived before today's date, August 9th 2001. This restriction made it challenging for scientists to access new ES cell lines, since at the time there were only 71 cell lines in 14 different laboratories around the world that met this criteria (Human Embryonic Stem Cell Policy…2009). By 2002, many U.S. scientists complained that of the 71 originally approved ES cell lines, many of them were damaged with mutations or were derived from the same donor, so scientists had far fewer cell lines to work with, seriously hindering ES cell research (Holden and Vogel, 2002).

Throughout his entire presidency, President Bush supported the policies that he enacted when first elected. The President supported the use of federal money for human ES cell lines that had already been established, but still did not allow federal funding to be given to research with newly derived lines. In spite of Bush's restrictions, in July of 2006, the Stem Cell Research Enhancement Act was passed by the United States Senate and Congress. The bill supported the use of federal funding for medical research involving all human embryonic stem cells, regardless of their date of creation (H.R. 810, 2005). The bill passed in both the senate and congress, but was vetoed by President Bush. President Bush stated that he vetoed the bill because he stood by his original mandate, and the bill proposed to overturn his previously established set of regulations, stating:

> *This bill would support the taking of innocent human life in the hope of finding medical benefits for others. It crosses a moral boundary that our decent society needs to respect. (H.R 810, ,2005)*

With his veto of the bill approved by Congress, President George W. Bush was mainly concerned with the possible loss of potential life. He felt that ES cells have the potential to save many lives, but alternative methods of derivation must be found (President Bush Delivers.. 2006). When the bill was sent back to the House, it failed to gain the 2/3 majority vote required to override the President's veto (HR 810, 2005), so the veto remained in effect.

Later in the summer of 2007, President Bush's policy placed on human ES cell was once again challenged by Congress. On June 20th, the President placed his second veto on a bill approved by Congress, stating that "Destroying human life in hopes of saving human life is not ethical" (Stolberg, 2007). The president also released an executive order entitled "Expanding Approved Stem Cell Lines in Ethically Responsible Ways", which explained in greater detail his concerns with human ES cells and possible resolutions that could possibly satisfy both sides of the argument. The president's main point of this order was to show his support for alternative methods of stem cell research, such as the use of induced pluripotent stem (iPS) cells, which may be able to produce a large variety of cells for treating diseases, while not destroying any embryos to derive them (Bush, 2007).

As the 2008 presidential election approached, some of the political figures showed support for human ES research. Democratic nominees Hillary Clinton and Barack Obama both showed positive support for the development of this type of research. Even John McCain and Rudolph W. Giuliani, two Republicans in the presidential running, were "generally supportive" (Stolberg, 2007). The generally supportive opinions of candidates for the 2009 presidency

foreshadowed a change in embryo research policies, along with a change in the American opinion on the use of this type of research for human ES cell research.

The Obama Administration and Stem Cells (2009-Present)

In January of 2009, the Democratic Nominee Barack Obama was sworn in as the 44th president of the United States. President Obama held drastically different positions on stem cells and embryos compared to previous presidents (President Barack Obama, 2012). On March 9th, 2009 President Obama issued executive order 13505, which revoked the harsh limitations on human ES cells previously supported by the Bush administration. Order 13505 extinguished the executive order that former President Bush ordered on June 20, 2007, which supported his previous law regarding embryo research in 2001. President Obama's order forced the NIH to release new guidelines for regulating embryo research within 120 days of the initial order signing (Removing Barriers..2009).

The NIH released their recommendations for human ES cell research on April 23, 2009. The new rules and regulations proposed by the NIH were much more liberal compared to the previous guidelines, and more closely resembled the policy recommended in 1994 by the NIH during the Clinton administration. The guidelines suggested the eligibility of human ES cell research for federal funding, and that the acquired embryonic cell lines had to be derived from an IVF created blastocyst, which was not being used for fertilization. In order to use these cells, the donor must also give consent for use in research (National Institutes of Health…2011). The new NIH guidelines provided ample opportunities for researchers, giving better access of embryonic stem cells to scientists. However, some researchers were disappointed with several research limitations that were still not lifted. For instance, the limitation stating that human embryos could

not be produced specifically for research, but had to be created by IVF methods (Wadman, 2009).

In August of 2010, District Chief Judge Royce C. Lamberth installed a preliminary injunction that attempted to halt President Obama's order 13505, intending to severely limit the availability of federal funding for human ES cell research. The injunction was placed when a lawsuit was filed against the NIH by groups who did not agree with the use of ES cells for any type of research (Cratty, 2010). One of the arguments that the lawsuit brought up is that Obama's new policy breaks the previous 1996 law passed by congress known as the Dickey-Wicker Amendment (Hsu & Leonnig, 2010). But in April of 2011, the injunction was overturned by a 2-1 vote in the court of appeals in Washington, D.C. The overturn of the Lamberth injunction allowed for a continuation of federally funded ES cell research, and also gave a good sign for the future of stem cell research in the United States (Appeals Court..2011).

Individual States and Stem Cells

Before the Obama administration took office, there had been relatively strict policies in the United States limiting federal ES cell research. During those lean times, several states began approving state funds for ES cell research. California, New Jersey, and Massachusetts strongly supported ES cell research with state funding, pushing away from the norm of many other states. These three states created propositions which provided funding for stem cell institutes in their respective states, supporting a varying array of private and public institutions (Embryonic and Fetal Research Laws..2008). These newly accepted state policies would help support ES research during the federal funding ban, and helped lead to larger public understanding of the possibilities that the use of stem cells holds.

The state of California has long shown support for ES cell research in the United States. There are several large research facilities with large stem cell research programs in California, such as the University of California System (UC) and Stanford University. In 2004, a proposal was written to create an institute that could create grants and distribute money fueled by the tax money of California citizens. The proposal known as Proposition 71 was approved in November of 2004, winning with 51% state wide approval (Proposition 71, 2004). Proposition 71 led to the establishment of the California Institute of Regenerative Medicine (CIRM). The Institute's purpose is to distribute grant money for research, create standards for research processes, and support all classifications of stem cell research in California. Proposition 71 provided 3 billion dollars to CIRM for redistribution among research institutes throughout California (Text of.. 2009). **Figure-1** illustrates various stem cell research institutions funded by the State of California through Proposition 71. The approval of California's Proposition 71 has enabled the availability of research funds for conducting a wide variety of research involving both embryonic and adult stem cells in public and private institutes all over California.

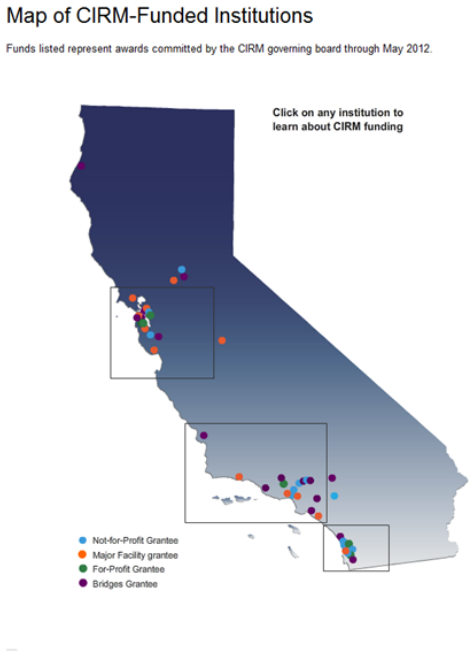

Figure-1: Map Showing the Locations of Proposition 71 Funded Stem Cell Institutions (Map of… 2012)

At approximately the same time California's Proposition 71 was passed, the state of New Jersey was also considering establishing their own institute for stem cell research, supported by state funds. In September of 2002, bill 1909 was first introduced to New Jersey State Senate (Senate Bill No. 1909, 2002). The bill, if signed, would provide funding for human ES cell research in New Jersey. Governor James E. McGreevey signed Bill 1909 into law in January of 2004 (McGreevey Signs..2004). In February of 2004, the governor of New Jersey declared his plan for the formation of an institute dedicated to the continuation of research of human ES cells in New Jersey. The Governor planned to provide Rutgers University and the University of Medicine and Dentistry of New Jersey, with 6.5 million dollars to establish a joint ES cell research institute (Mansnerus, 2004). The New Jersey legislature approved this plan on June 25, 2004.

In May of 2005, the Massachusetts Senate and House of Representatives passed a bill intended to expand human ES cell research opportunities in the Commonwealth of Massachusetts. The bill supported the expansion of research opportunities, by "permitting research and clinical applications involving the derivation and use of human embryonic stem cells", although the new law would ban human reproductive cloning in the state (An Act Enhancing.. 2005). The Bill was passed in the Massachusetts House of Representatives 119 supporting votes to 38 opposing, and in the state senate by 34 votes to 2. Despite support by both the House of Representatives and state senate, Governor Mitt Romney attempted to install four new amendments which would restrict human ES cell research. The amendments intended to ban the creation of embryos specifically for research, redefine the "beginning of life" criteria, make it more difficult for woman to receive payment for donating eggs, and restrict the donation of embryos. In 2007, after Governor Deval Patrick was sworn into office, the controversial limits

placed on stem cell research were removed, when voted on by the Public Health Council. The eradication of the previously enacted policies brought the state of Massachusetts back to a more open policy concerning stem cell research (Smith, 2007). The removal of Romney's previously restricting policies allowed for institutes throughout the Commonwealth to reinitialize their human ES cell research programs, and led to the establishment of the University of Massachusetts Human Stem Cell Bank and Registry in Shrewsbury, MA in November of 2008. The development of similar stem cell banks across the Commonwealth, which produce both human ES and adult stem cell lines, illustrates that Massachusetts is moving towards greater support of human ES cell research. The improvement is also seen by an increase in local government representatives and an increased public awareness of the benefits of human ES cell research (Policies and Procedures..2011).

International Stem Cell Laws

The United States is not the only country dealing with controversial political clashes on the use of embryos for research. Nations outside of the United States began to establish laws and policies for regulating human embryo research around the same time as the United States. Countries such as Sweden and Japan currently allow human ES cell research, while countries like Germany have much stricter regulations (Wiedemann et al., 2004). Different cultures and ethical backgrounds present in various countries play a significant role in the formation of their laws regulating human ES cell research.

Sweden did not have any official guidelines for human ES cell research until 2002. The Swedish Research Council released their guidelines in December of 2001, which were then passed into law in January of 2002. The laws allowed for the collection of spare embryos which

were to be discarded after IVF treatment. Therapeutic cloning was acceptable, but the creation of embryos specifically for research was not allowed (Zeiler, 2002). There are many different stem cell research groups working throughout Sweden. For instance, at Lund University there are 24 groups alone, working on research in the fields of "cancer, developmental biology, hematopoiesis and neuroscience" using stem cells. In addition there are other groups throughout the country, including the Centre for Brain Repair and Rehabilitation at Gothenburg University, and private companies such as Cellatris and NeuroNova (Nordforsk Policy Briefs, 2007). The existing human ES cell policies in Sweden classify the country as one of the most accepting in the world.

The deliberation of stem cell policies seen in the western world is also reflected in many Asian countries. In Japan, a set of laws approved in November of 2000, known as "The Law Concerning Regulation to Human Cloning Techniques and Other Similar Techniques", proposed new regulations and prohibitions on human ES research. Prior to November of 2000, Japan had no specific laws concerning human cloning or ES cell research. In September of 2001, Japan's Ministry of Education, Science and Technology enacted several new policies that restricted human ES research. The use of IVF embryos for ES cell research was restricted to only embryos that were unused or left over from IVF treatments and would otherwise be thrown away (Walters, n.d.). In 2009, several of the regulations were relaxed by the Council for Science and Technology Policy, banning reproductive cloning but allowing somatic cell nuclear transfer for therapeutic cloning (The Witherspoon Council..2012). These sets of policies have brought Japan to a very similar position as many other research intensive countries around the world.

The German government has placed far more restrictive regulations on the availability of human ES cell research opportunities. The German Embryo Protection Act of 1990 outlawed the

production of ES cells isolated from otherwise discarded IVF-embryos in the country. In April of 2002, the "Embryonic Stem Cell Act" was passed in parliament which allowed the import of human ES cell lines for the use in research, but the cell lines had to be derived before January 1st 2002 (Oduncu, 2003). The law was later updated in 2008, to allow for the use of ES cell lines produced before May 1st 2007 (Germany Eases..2008). Since then, there have not been many newly developed opportunities for human ES cell research. In October of 2011, the European Court of Justice ruled that ES cell research could not be patented within the European Union. Oliver Brustle, who was part of the opposition, said this outcome was "a disaster for Europe" (Callaway, 2011). The newly installed ban will make it difficult for researchers to gain support from large profit making companies within Germany and throughout the Europe Union (Callaway, 2011).

Chapter-4 Bibliography

An Act Enhancing Regenerative Medicine in the Commonwealth (2005, May). Retrieved July 30, 2012, from The 187th General Court of The Commonwealth of Massachusetts: http://www.malegislature.gov/Laws/SessionLaws/Acts/2005/Chapter27

Appeals Court Overturns Stem Cell Resarch Ban (2011, April 29). Retrieved July 25, 2012, from CBS News: http://www.cbsnews.com/2100-204_162-20058583.html

Barnes DW, Stevenson RE (1989) Meeting Report: Human Fetal Tissue Transplantation Research Panel. *In Vitro Cell and Developmental Biology*, 25(1): 6-8.

BBC News (1978) 1978: First Test Tube Baby Born. http://news.bbc.co.uk/onthisday/hi/dates/stories/july/25/newsid_2499000/2499411.stm

Beschloss M, Sidey H (2009) George W. Bush. Retrieved July 15, 2012, from: http://www.whitehouse.gov/about/presidents/georgewbush

Bush, George (2001) Radio Address by the President to the Nation. Whitehouse Archives. http://georgewbush-whitehouse.archives.gov/news/releases/2001/08/20010811-1.html

Bush, George W (2007, June 20). *Executive Order: Expanding Approved Stem Cell Lines in Ethically Responsible Ways.* Retrieved July 18, 2012, from The White House: http://georgewbush-whitehouse.archives.gov/news/releases/2007/06/20070620-6.html

Callaway E (2011, October 11). European Court Bans Patents Based on Emryonic Stem Cells. Retrieved August 1, 2012, from Nature: http://www.nature.com/news/2011/111018/full/news.2011.597.html

Cratty C (2010, August 24). Goverment will Appeal Injunction Against Stem Cell Funding. Retrieved July 25, 2012, from CNN: http://articles.cnn.com/2010-08-24/us/stem.cell.funding_1_dickey-wicker-amendment-cell-research-cell-funding?_s=PM:US

Dunn K (2005) The Politics of Stem Cells. Retrieved July 12, 2012, from NOVA Science Now: http://www.pbs.org/wgbh/nova/body/stem-cells-politics.html

Embryonic and Fetal Research Laws: Stem Cell Research. (2008, January). Retrieved July 25, 2012, from National Conference of State Legislatures : http://www.ncsl.org/issues-research/health/embryonic-and-fetal-research-laws.aspx

Germany Eases Ban on Embryonic Stem Cell Lines. (2008, April 16). Retrieved August 1, 2012, from Nature: http://www.nature.com/news/2008/080416/full/452796a.html

How Legislation on Fertility Treatment Developed. (2009, March 17). Retrieved August 1, 2012, from Human Fertilisation Embryology Authority: http://www.hfea.gov.uk/1319.html

HR 810 (109th): Stem Cell Research Enhancement Act of 2005. (2005). Retrieved July 15, 2012, from Govtrack.us (Database of Federal Legislation): http://www.govtrack.us/congress/bills/109/hr810

Hsu SS, & Leonnig C (2010, August 24). Stem Cell Judge Royce Lamberth No Stranger to Controversy, Independence. *The Washington Post*.

Human Embryonic Stem Cell Policy Under Former President Bush (Aug. 9, 2001–Mar. 9, 2009). (2009, March 10). Retrieved July 15, 2012, from National Insitutes of Health: http://stemcells.nih.gov/policy/2001policy.htm

Janson-Smith D (2002, July 19). The Human Fertilisation and Embryology Act *(1990)*. Retrieved August 1, 2012, from The Human Genome: http://genome.wellcome.ac.uk/doc_WTD021016.html

John R K, Brade JV, Cooke RE, Height DI, Jonsen AR, King P, et al. (1975) *Report and Recommendations: Research on the Fetus.* Retrieved July 17, 2012, from http://videocast.nih.gov/pdf/ohrp_research_on_fetus.pdf

Kearl, Megan (2010) Dickey-Wicker Amendment. Embryo Project Encyclopedia. ISSN: 1940-5030.

Kiessling AA (2010) The History of the Dickey-Wicker Amendment. *Time Magazine*, 37(1).

Kington, Raynard S (2011) National Institutes of Health Guidelines on Human Stem Cell Research. Retrieved July 23, 2012, National Institute of Health: http://stemcells.nih.gov/policy/2009guidelines.htm

Mansnerus L (2004, Febuary 21). New Jersey Govenor Puts Stem Cell Research in Budget Plan. Retrieved July 27, 2012, from New York Times: http://www.nytimes.com/2004/02/21/nyregion/21jersey.html

Map of CIRM-Funded Institutions (2012, May). Retrieved July 26, 2012, from California Institute for Regenerative Medicine: http://www.cirm.ca.gov/our-funding/where-our-funding-goes/interactive-map/map-cirm-funded-institutions-california

McGreevey Signs Landmark Stem Cell Research Act (2004, January 4) Retrieved July 18, 2012, from The State of New Jersey: http://www.state.nj.us/cgi-bin/governor/njnewsline/view_article_archives.pl?id=1668

Madrazo I, Leon V, Torres C, et al. (1988) Transplantation of fetal substantia nigra and adrenal medulla to the caudate nucleus in two patients with Parkinson's disease. *New England Journal of Medicine*, 318: 51.

Nordforsk Policy Briefs (2007) Stem Cell Research in the Nordic Countries. http://www.nordforsk.org/en/publikasjoner/policy-brief-2

Oduncu FS (2003) Stem Cell Research in Germany: Ethics of Healing Vs. Human Dignity. *Medicine, Heath Care and Philosophy*, *6*(1), 5-16.

Policies and Procedures (UMass Human Stem Cell Bank and Registry). (2011, April 2). Retrieved July 30, 2012, from Umass Medical School: http://www.umassmed.edu/uploadedFiles/MHSCB/Bank%20Policies%20Procedures%202%20U.pdf

Proposition 71 (2004, November 2) Retrieved July 25, 2012, from UC Berkeley: Institute of Governmental Studies: http://igs.berkeley.edu/library/research/quickhelp/elections/2004general/htProp71StemCell.html

President Barack Obama (2012) Retreived July 23, 2012, from The White House: http://www.whitehouse.gov/administration/president-obama

President Bush Delivers Remarks on Stem Cell Research Policy (2006, July 19) Retrieved July

15, 2012, from The Washington Post: http://www.washingtonpost.com/wp-dyn/content/article/2006/07/19/AR2006071901223.html

Removing Barriers to Responsible Scientific Research Involving Human Stem Cells (2009, March 9) Retreived July 23, 2012 from the White House: http://www.whitehouse.gov/the-press-office/removing-barriers-responsible-scientific-research-involving-human-stem-cells

Rewerski P (2007). The Need For A New U.S. Stem Cell Research Policy: A Comparative Look at International Stem Cell Research Laws. *University of Illinois Journal of Law, Technology& Policy, 2*, 415-431.

Roe v. Wade (2012) Retrieved July 05, 2012, from Enccyclopaedia Britannica Online Academic Adition: http://www.britannica.com/EBchecked/topic/506705/Roe-v-Wade

Senate, No. 1909 (2002, September 30) Retrieved July 18, 2012, from New Jersey Legislature: http://www.njleg.state.nj.us/2002/Bills/S2000/1909_R1.PDF

Sharpiro, H. T, Backlar, P, Brito, A, Capron, A. M, Cassel, E. J, Charo, R. A, et al. (1999, September) Ethical Issues In Human Stem Cell Research. Retrieved July 17, 2012, from Bioethics Research Library at Georgetown University: http://bioethics.georgetown.edu/pcbe/reports/past_commissions/nbac_stemcell1.pdf

Smith S (2007, October 11). Health Council Repeals Romney Limit on Stem Cell Research. Retrieved August 1, 2012, from The Boston Globe: http://www.boston.com/news/local/articles/2007/10/11/health_council_repeals_romney_limit_on_stem_cell_research/

Stith-Coleman, Irene (1998) Human Embryo Research. The Library of Congress. Retreivd July 20, 2012 from: http://www.law.umaryland.edu/marshall/crsreports/crsdocuments/95-910_STM.pdf

Stolberg SG (2007, June 21) Bush Vetoes Measure on Stem Cell Research. *The New York Times*, p. A21.

Text of Propositon 71 (2009) Retrieved July 26, 2012, from California Institute for Regenerative Medicine: http://www.cirm.ca.gov/AboutCIRM_Prop71

The Clinton Presidency: Eight Years of Peace, Progress and Prosperity (2012) Retrieved July 11, 2012, from The White House: The Clinton-Gore Administration: http://clinton5.nara.gov/WH/Accomplishments/eightyears-02.html

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1975) Report and Recommendations: Report on the Fetus.

http://bioethics.georgetown.edu/pcbe/reports/past_commissions/research_fetus.pdf.

The Witherspoon Council on Ethics and the Integrity of Science, "Appendix E: Overview of International Human Embryonic Stem Cell Laws," *The New Atlantis*, Number 34, Winter 2012, pp. 129-146

Thomas ED, Lochte HL, Lu WC, et al. (1957) Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy. *New England Journal of Medicine*, 257(11): 496-496.

Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, et al. (1998, November 08) Embryonic Stem Cell Lines Derived from Human Blastocyts. *Science*, 282(5391): 1145-1147.

Wadman M (2009, April 17). NIH Announces Draft Stem-Cell Guidelines. Retrieved July 28, 2012, from Nature: http://www.nature.com/news/2009/090417/full/news.2009.373.html

Walters L (n.d.). Human Embryonic Stem Cell Research: An Intercultural Perspective . Retrieved August 1, 2012, from Project Muse: The John's Hopkins University Press: http://science.jburroughs.org/mbahe/BioEthics/Articles/Walters_stem_cells.pdf

Wertz D (2002) Embryo and Stem Cell Research in the United States: History and Politics. *Nature*, 9(11): 674-678.

Wiedemann PM, Simon J, Schicktanz S, & Tannert C (2004, October). The Future of Stem Cell Research in Germany. *EMBO Reports, 5*(10), 927-931.

Zeiler K (2002, December). *Sweden, Stem Cell Research and Ethics: Two Weaknesses of the Debate*. Retrieved August 1, 2012, from Evangelical Lutheran Church in America: http://www.elca.org/What-We-Believe/Social-Issues/Journal-of-Lutheran-Ethics/Issues/December-2002/Sweden-Stem-Cell-Research-and-Ethics-Two-Weaknesses-of-the-Debate.aspx

PROJECT CONCLUSIONS

Stem cell research raises many ethical concerns and must abide by strict regulations. The use of embryonic stem (ES) cells is at the forefront of the ethical debates, as isolating those cells destroys a 5-day old IVF blastocyst. Contrary to popular beliefs, the destruction of human embryos for research does not involve an *in vivo* procedure, nor does it involve aborted fetuses. The current laws under the Obama administration allow only the use of surplus embryos originally prepared for reproductive purposes from *in vitro* fertilization clinics for research purposes. This is a common misconception when discussing the "killing" of human embryos, as the public often believes this involves an abortion. This is what the authors of this project believe makes human ES cell research ethical. If these surplus IVF embryos are going to be discarded anyways, then the use of them for future medical breakthroughs trumps the ethical arguments against their use.

The authors also agree with the current legislation under the Obama administration forbidding the payment of money to egg donors, as this might force women to undergo a risky medical procedure solely because they are poor. The only way ES cells should be derived is by obtaining them from surplus IVF embryos. But an embryo should not be killed if families still plan on using it for IVF procedures.

Research on iPS cells should undoubtedly be continued and perfected because the use of such stem cells raises few ethical issues and yet these cells may have the potential to be pluripotent just like ES cells. We agree with the recent protocols that omit the *c-Myc* gene from the mixture of reprogramming genes used in the reprogramming procedure to minimize the potential of cancer formation. We support further research on iPS cells to determine whether the

reports on DNA damage are rare or widespread, and to determine the true potency of the cells. iPS cells, once fully understood, and adult stem cells should be used over embryonic stem cell as often as possible. If a particular type of adult stem cell is found to be sufficient for treating a particular disease, then that type of stem cell should be used instead of ES cells if possible.

The authors strongly agree with Presidents Clinton and Obama policies concerning the use of only spare IVF embryos, and no pay for egg and sperm donations. The National Bioethics Advisory Commission, in September 1999, released its guidelines supporting this policy. We also agree with the Obama administration's further step of requiring consent from the donating family of the IVF embryo. So as of right now, we feel the United States has the right balance of laws regulating embryo and ES cell use.